

TASK FORCE ON COUNTERMEASURES

FINAL REPORT



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NASA TASK FORCE ON COUNTERMEASURES

Introduction

In the Fall of 1995 a subgroup of the Life and Microgravity Sciences and Applications Advisory Committee (LMSAAC) was established for a one year period in which to a) assess the status of countermeasures routinely used by NASA to counteract the deleterious physiological changes in humans that occur in response to the microgravity environment involving space flight; and b) determine appropriate recommendations concerning essential research and development activities relevant to enhancing the effectiveness of the countermeasure program. Specifically, the Countermeasures Task Force (CTF) was charged with:

- Surveying the efficacy and appropriateness of existing countermeasures and the ongoing research program to develop countermeasures for long duration missions.
- Evaluate the adequacy of existing data bases.
- Evaluate NASA's plans in the area of countermeasures as currently constituted. For example, are there lessons to be learned from the Space Shuttle, Skylab and Russian Programs that should change the current program.
- Recommend both appropriate short term and long term changes for improving the countermeasure program and its implementation as well as recommend new and innovative research activities.
- Provide feedback concerning the quality and direction of the Medical Policies and Requirements Document formulated by the Medical Policy Board of NASA as a blue print for sponsored national and international missions involving humans in space.

Organization of the Task Force Committee:

On January 31, 1996 the CTF convened via teleconference and was formally charged by NASA Headquarters. At that meeting it was agreed that the committee would be formed into four subgroups to deal with countermeasure and operational issues pertaining to 1) the cardiovascular system; 2) the neuromuscular system including motor performance; 3) the bone and connective tissue system; and 4) clinical medicine including neurological issues. Subsequently, two additional subgroups were formed to deal specifically with neurological issues and the area of behavior and performance.

Following the initial teleconference, the committee formally met twice at the Center for Advanced Space Studies in Houston, Texas. The first meeting occurred on April 11-12, 1996 and was followed by a second meeting on June 27-28, 1996 in order to review the status of countermeasures currently used by NASA and to delineate the scope of the report as detailed in the sections presented below. The membership of the Task Force is provided in Appendix A.

Background:

For approximately 35 years, humans (and to a lesser degree other mammalian species) have been exposed to the microgravity environment of space flight for varying duration lasting from days to weeks to several months. During the course of human exposure to this unique environment a number of adaptations have been observed both inflight and post-flight. These include, but are not limited to, the following: inflight - vestibular and oculomotor dysfunction, a reduction in the intrinsic strength and

power output of skeletal muscle, bone atrophy, and changes in connective tissue function; post-flight - reductions in work capacity and aerobic metabolic potential during the performance of high intensity exercise, cardiovascular deconditioning as manifest chiefly by the inability to regulate blood pressure in an upright posture, and balance and sensory motor disruption.

These deficits, both individually and in combination with one another, have had a significant negative impact on the functional and structural integrity of mammals, including humans, such that a major objective in both the NASA and Russian Space Programs has been to seek countermeasures to either fully ameliorate or minimize these deficits. The overall effectiveness of the countermeasures program has been difficult to assess for a number of reasons.

First, there has been a long history of policies and procedures designed to prevent any potential deleterious effects of space flight from impacting the functional integrity of humans upon return from the space environment. Consequently, all individuals exposed to space for a significant duration (several days) have undergone some type of countermeasure activity. This strategy has precluded the quantification of the maximal physiologic change that would occur during spaceflight. Second, often there have been numerous countermeasures simultaneously imposed, which has made it difficult to sort out which one(s) is more effective in reducing a specific deficit. Finally, there is a growing body of evidence to suggest that inappropriate strategies may have been utilized in attacking certain problems thereby reducing the success of correcting other deficits. Thus, as NASA prepares for the space station era in which humans routinely will be spending significantly longer periods (months) in space, it is essential that a complete analysis of the countermeasure program be undertaken at the present time.

Organization of the Report

In formulating the report, the various subcommittees of the CTF used two primary avenues of analyzing the current information pertaining to countermeasures: 1) a thorough review of the current literature (including NASA reports) describing the effects of space flight on physiological processes including the effectiveness of countermeasures; and 2) interaction with the program managers and scientists within NASA involved in both designing and implementing the current countermeasure strategies. Based on these deliberations the report is centered around a series of discipline reports that address the following generic issues: 1) the nature of the problem; 2) the status of current countermeasures to the problem; 3) concerns relevant to the problem; 4) recommendations to improve countermeasures for a given discipline; and 5) milestones and overarching issues relevant to the integrated countermeasures program.

Presented below are the individual discipline reports. Following the presentation of these reports are a series of presentations in the appendix that are discipline specific and designed to further document the scope of the discipline recommendations.

Skeletal Muscle Discipline Report on Countermeasures

I. Nature of the Problem

Accumulated evidence, based on information gathered on space flight missions and ground based models involving both humans and animals, clearly suggests that exposure to states of unloading

(microgravity conditions) for varying duration (days to weeks to months) induces a variety of adaptations in the intrinsic structural and functional properties of skeletal muscle. These alterations or deficits include the following structural, biochemical/molecular, physiological, and biomechanical properties.

- 1) Atrophy of both slow-twitch and fast-twitch muscles (fibers) comprising the lower extremity and trunk musculature.
- 2) A change in contractile protein isoform expression in a select population of slow-type fibers reflecting a faster phenotype for controlling both cross bridge and calcium cycling processes, i.e., the primary pathways for energy consumption in performing mechanical activity.
- 3) Corresponding changes in the functional properties of the muscle manifesting a speeding in the shortening and relaxing properties of the muscle.
- 4) A reduction in both the absolute and relative force and power generating properties of fiber-types comprising antigravity and locomotor skeletal muscle.
- 5) A shift in the intrinsic activation patterns of antigravity muscles whereby a greater frequency of neural activation is required to generate submaximal force output of the muscle. These alterations are likely impacted further by alterations in the metabolic and functional properties of dorsal root ganglia cells in small motoneurons, which could impact the intricate function of both sensory and motoneurons linked to the skeletal muscle system.
- 6) A shift in the intrinsic substrate utilization profiles of the muscle whereby the capacity to metabolize fat as a primary fuel is reduced relative to that of carbohydrate. Such a shift in profile could potentially compromise the intrinsic endurance properties of the muscle.

Collectively, the above listed alterations provide the underlying factors contributing to the well documented profile whereby individuals following prolonged space flight (and/or ground based states of unloading) have reduced strength, power, and musculoskeletal endurance as well as a reduced capability of performing routine motor activities requiring both stability and fine motor skills. Presently, it is uncertain as to what extent these functional deficits a) impair one's ability to perform strenuous extravehicular activity, particularly after more prolonged exposure to microgravity, and b) deleteriously affect one's ability to perform high intensity egress activities in the event of an emergency upon landing. Further, in the absence of adequate control data (i.e., information obtained on individuals in the absence of countermeasures) on human subjects exposed to microgravity, it is presently unknown as to what extent these deficits can be ultimately manifest.

II. Countermeasures to the Problem

The successful performance of any movement activity of varying intensity relies upon three important properties of neuromotor function:

- 1) the ability to coordinate contractile activity across the muscle groups involved in that task (the property of motor unit recruitment and coordination);

2) the ability to generate adequate force (and power) to accomplish the movement and/or work requirements (the property of strength);

3) the ability to sustain the activity over a period of time (the property of endurance).

Based on the available evidence, it appears that the countermeasure strategies used to date for maintaining the skeletal muscle system in microgravity have been biased to maintaining muscular endurance (chiefly as an outgrowth of maintaining cardiovascular fitness) with relatively less attention focused on maintaining muscle strength and motor control. This conclusion is based on the types of exercise equipment and exercise paradigms that have been used during space flight, i.e., the use of treadmills, rowing devices, and cycle ergometers. While these activities are largely suitable for providing adequate stimuli to the cardiovascular system, it is uncertain as to how effective they have been in maintaining muscle performance. The concern is that routine activities of running, cycling and rowing are manifest as “high frequency and low force” activities, which theoretically should enhance the endurance of the muscle. However, in order to prevent muscle atrophy and minimize the loss of strength and power of the musculature (which are influenced by both muscle mass and neural factors), activities which require maximal or near maximal force output of the muscle (i.e., high forces and low frequencies) are required. The activities presently used are likely imposing force requirements on the muscle groups in the range of only 25-35% of what is thought to be required.

While recent reports concerning the exercise programs designed more specifically for the Extended Duration Orbiter Program are beginning to address the importance of incorporating heavy resistance paradigms as part of the countermeasure strategic plan, this is a strategy that only recently has received any attention, but one that needs to be brought to the forefront. This conclusion is based on the fact that in spite of the large volume of exercise that has been routinely performed by individuals on extended orbit in both the American and Russian Space Programs the overwhelming evidence indicates that the exercise paradigms and other countermeasure strategies have been marginally successful, at most, in preventing deficits in muscle structure and function. Furthermore, in ground based models involving animals, it is most apparent that exercise programs of the endurance type are markedly inefficient compared to heavy resistance paradigms in preventing the marked degree of muscle atrophy and loss of strength that occurs in response to muscle unloading.

III. Concerns

While it is recognized that endurance exercise continues to be an important constituent in the overall health maintenance for prolonged space flight, NASA must re-examine the almost exclusive dependence on aerobic exercise countermeasures and establish a new set of priorities in its countermeasures program. These priorities need to be better aimed at targeting a broader scope of the physiological systems of the body, including a greater focus on the skeletal muscle system.

At the present time there is little data indicating which muscles will be needed in work performed during extra vehicular activity (i.e., arms, shoulders, upper chest) nor is there assurance that appropriate countermeasures are in place that sufficiently maintain skeletal muscle structural and functional properties necessary to support the work capacity for extravehicular activity necessary for the construction of space station. This activity will require exercise tasks highly dependent on sustained work capacity under loading conditions confounded by the cumbersome space suits that are necessary for extravehicular activity.

Further, there is little information available that defines the minimal (essential) level of strength, power, agility/motor skill, and endurance necessary for assuring astronaut capability of successfully performing either work necessary to begin exploration of a distant planet, nor emergency egress activity during the landing phase of a mission following prolonged astronaut exposure to microgravity. Hence, it is uncertain whether individuals have the performance capability to handle such events.

IV. Recommendations

- 1) Heavy resistance training paradigms, aimed at eliciting maximal force production of key muscle groups supporting posture and locomotion, need to be initiated as soon as possible as an integral strategy for maintaining the skeletal muscle system. As an initial approach, strategies similar to those currently used on earth to optimize strength and enhance muscle enlargement should be used at the outset of such a program.
- 2) NASA Life Sciences and Operational Medical Programs should explore the utilization of currently available equipment that is capable of meeting the needs of such an exercise program rather than looking to build new equipment devices.
- 3) Exercise of high frequency-low force, i.e., the endurance type, should be continued as part of the conditioning regimen. Further, activities which impact on neuromotor skills to support posture, balance vestibular-oculomotor activities also need to be incorporated as part of the training program.
- 4) NASA needs to assess the level of physical skills (strength, power, endurance, motor control etc.) necessary to perform the type of work used in EVA, distant planetary landing, and emergency egress activity likely encountered by astronauts. These levels of skill should serve as the guideline(s) for establishing the level of fitness to be maintained by the exercise programs used in the countermeasures program. It seems reasonable to expect that all training programs will not maintain individuals at their respective pre-flight physical capacity; and thus more reasonable performance standards need to be sought.
- 5) Long term goals of NASA, in conjunction with the Countermeasures Program, need to establish basic and applied research that identifies the mechanisms of muscle wasting and to seek more effective countermeasures for preserving skeletal muscle homeostasis. Research in this area should focus on strategies to increase the effectiveness of physical activity via studies on the interaction of physical activity, pharmacological, and hormonal/growth factor approaches to understanding muscle plasticity.

V. Overarching Issues

This discipline endorses recommendations of the other disciplines covered in this report which support a greater focus on including research on 1) establishing better nutritional requirements and standards for astronauts; and 2) the establishment of an exercise countermeasure strategy that integrates activities supporting cardiovascular, vestibular and neuromotor, and musculoskeletal objectives. Since it is unlikely that there is an all encompassing type of exercise capable of counteracting microgravity-induced deficiencies in these systems, studies should be undertaken to take advantage of the technologies currently being developed to produce forms of artificial gravity via the use of exercise-cycling and other exercise devices that have the potential to transiently generate g-forces known to positively impact on the cardiovascular, vestibular, muscle and bone systems while simultaneously providing an exercise stimulus mimicking that currently seen with most conventional devices. Since technology to support

this type of activity is rapidly emerging with design configurations that are feasible for incorporation into the space station modules, appropriate research to verify that intermittent use will protect without causing additional physiologic problems is needed.

Bone and Connective Tissue Discipline Report on Countermeasures

I. Nature of the Problem

Bone mass, mineral metabolism and connective tissue changes occur in humans during space flight. Physiologic changes occur as early as one week and continue for more than a year in microgravity. These changes may limit long duration spaceflight if the changes harm space faring individuals either during long duration stays in space, on immediate return to earth or other planetary bodies, or become a “career” hazard which could accelerate the “aging” process. NASA must establish a program to minimize or prevent the changes and/or establish proven rehabilitation programs to restore the human space traveler to their preflight physiologic state. The well documented alterations or deficits reported in humans are listed as follows along with potential problems that may occur to the individuals involved:

1. Bone/mineral loss occurs when body mass is lost. Maintaining body mass appears to be important in maintaining overall bone mass. However, site-specific bone changes are-observed even when body mass is maintained.

Concerns include osteoporotic fractures and: decreased bone strength, decreased muscle and strength performance, decreased ability to maintain upright balance with falls resulting in bone fractures.

2. Urinary calcium increases rapidly to approximately 100% above preflight levels, plateauing after 30 days of flight and remaining above the preflight baseline for the duration of the flight..

Concerns include increased risk of kidney stones.

3. Progressive fecal calcium loss may occur; indications of such a change were reported during the Skylab IV mission, indicating that at least over 84 days of spaceflight either gastrointestinal (GI) calcium absorption is continuing to decline, calcium secretion into the GI tract is increasing, or both.

Concerns include decreased GI absorption of other minerals and nutrients related to the changes in calcium metabolism.

4. Calcium balance reaches a nadir of ~200 mg/d within 2 months of continuous spaceflight.

Concerns include bone loss and depletion of calcium which is critical for many physiological functions. If GI absorption of calcium is suppressed and renal excretion of calcium continues to be elevated during spaceflight, then calcium and bone loss over long duration spaceflights could be mission limiting.

5. Elevation in serum calcium occurs during space flight, although the values are within the normal clinical range.

Concerns include the risk of hypercalcemia during periods of dehydration or illness and the resultant potential for metastatic calcification, and brain and heart dysfunction.

6. Decreased levels of systemic calciotropic hormones may occur.

Concerns include decreased absorption of calcium from the gut, increased calcium excretion through the kidney, and a skeletal system that is metabolically sluggish possibly causing delayed readaptation postflight and depletion of calcium stores inflight.

7. DEXA scans show bone loss in the lower spine and hip, averaging about 1.2% loss per month of space flight at these sites. Similar losses in the posterior elements of the vertebrae were shown using CT technology. Muscle atrophy may occur at the sites of bone loss. No changes have been reported in the arms and upper torso.

Concerns include potential balance and locomotion problems with fractures of weight-bearing bones upon entry into a higher gravity environment.

8. Height increases during space flight which may be related to either an increase in the size of the intervertebral discs or a decrease in the curvature of the spine.

Concerns include physical changes to the intervertebral discs which may increase the risk of rupture, back pain and neurologic complications. These changes might be potential recovery risks both for the short term, i.e. immediate on return to a planetary body or long term i.e. increased “aging”.

9. Inflight exercise may help ameliorate specific bone loss, e.g. the calcaneus, but has not successfully prevented bone loss or prevent the urinary calcium increases.

Concerns include the lack of effectiveness of the type and amount of activity currently prescribed; in fact, strenuous exercise which does not properly load the musculoskeletal system could even exaggerate bone loss unless dietary intake is adequate.

10. The time course for recovery of bone mass to preflight levels is still not known although preliminary data suggest that recovery takes up to 2 years. Serum and urinary calcium appear to normalize rapidly following space flight.

Concerns include the possibility that trabeculae once lost may not be replaceable leading to accelerated “aging” and decreased bone strength. Also, multiple missions might compound the bone loss.

II. Countermeasures to the Problem.

Successful countermeasures for maintaining calcium/bone/connective tissue homeostasis during long-duration space flight are dependent upon an appropriate diet and an inflight exercise regime that maintains muscle and bone mass. Nutritional requirements have not been established for microgravity environments. It is possible that substantial changes in dietary intakes are required in space compared to earth. Additionally current Mir exercise programs have been unsuccessful in inhibiting the flight related bone loss.

Many factors associated with space flight, in addition to microgravity and/or changes in physical loading forces, may affect skeletal adaptation and calcium homeostasis. Prior physical fitness and the predominate type of exercise performed may influence initial bone mass and remodeling forces. Caloric

balance influences the amount of energy available for anabolic processes, including bone matrix synthesis. Nitrogen balance reflects the quantity of amino acids retained by the body, which may be used for bone matrix synthesis. Finally dietary calcium, other necessary minerals, and adequate vitamin D will affect bone mineral deposition in new bone and the rate of resorption in older bone. Therefore diet is a critical component of bone/mineral metabolism/connective tissue responses. Unless adequate diets can be provided to maintain body mass and to minimize mineral excretion, whole body mineral loss will be exaggerated due to diet. Increases in dietary calcium during space flight above a yet unknown quantity are probably not necessary and may be contraindicated if increased urinary and blood calcium occur. Microgravity-induced bone loss continues to be a significant physiologic adaptation that can have detrimental short-term and potentially long-term effects on astronauts. Therefore, there continues to be a need to better understand the mechanisms involved in microgravity-induced loss and to develop either countermeasures to prevent it or successful rehabilitation programs.

From a hormonal perspective there is strong evidence to suggest that the mobilization of calcium from the skeleton alters the PTH-vitamin D axis. This alteration ultimately results in decreased intestinal calcium absorption and the continual removal of calcium from the bone to satisfy the body's calcium requirements for its metabolic functions. When considering the calcium intake of astronauts, this issue needs to be carefully considered. It is important that the astronauts have an adequate dietary source of calcium probably in the range of 800 to 1000 mg/day along with an adequate source of vitamin D that approaches 600 IU/day. Consideration should be given to the incorporation of a simulated sunlight source for long-duration space flight as a mechanism to passively provide astronauts with their vitamin D requirement. The solar simulated light source may also provide them with other benefits including a feeling of well being. It is unclear at the present time if the use of the vitamin D hormone (calcitriol) to enhance the efficiency of intestinal calcium absorption would be wise. Although calcitriol will definitely enhance intestinal calcium absorption, any decrease in bone formation would minimize the ability of the bone to use this calcium. If less calcium goes into bone, then the increased absorption of calcium into the blood can increase the risk for kidney stones, hypercalcemia and soft tissue calcifications. Supplementation of the diet with calcitriol to enhance the efficiency of intestinal calcium absorption during inactivity without causing other problems has not been validated.

A variety of other hormones could impact both calcium and bone metabolism. Glucocorticoids can significantly alter calcium and bone metabolism. Strong evidence suggests that cortisol levels are increased in astronauts especially during the early part of their flight. Whether this is due to the stress of the flight or other causes is unclear. There may be other hormonal factors such as IGF and its binding proteins that could be altered in microgravity and this requires further investigation. Other local bone factors which control bone turnover have not yet been studied in humans during space flight and it is unknown if the changes in these factors could cause or contribute to the bone atrophy.

III. Concerns

NASA does not have a required preflight fitness level. "Human exploration in space requires the ability to maintain crew health and performance in spacecraft, during extravehicular activities, on planetary surfaces, and upon return to Earth." (Strategic Considerations for Support of Humans in Space and Moon/Mars Exploration Missions, Vol 1, Page 1, NASA Advisory Council, Aerospace Medicine Advisory Committee, June 1992). If the goal of the human flight program is to assure health, productivity, and safety of the crews both in space and upon return to a gravity environment, it may not require maintaining preflight physical status.

One valid concern is the apparent focus of many recommendations on establishing preflight, and maintaining inflight, an elite physical status. The recommendations have been correctly based on what appears to be effective on Earth, i.e., an increase in bone and connective tissue mass such that one can afford to lose some mass over time. However, these recommendations may be counterproductive for spaceflight. The establishing of an elite physical fitness status may increase the metabolic requirements of an individual and make that individual more susceptible to changes that occur under conditions of decreased biomechanical loading. The unique environment of space requires unique thoughts and countermeasures that may be different from those that would be recommended for individuals remaining on Earth. For example, swimming might provide better preparation than jogging since the muscles used and motions learned will be similar to those used in flight. Yet, jogging or high impact loading at 1G, that is often suggested for preflight training, produces loads that are virtually impossible to reproduce in flight with available exercise equipment. The Russians provide individual trainers for their cosmonauts and recommend swimming for preflight conditioning.

Caloric intake of Shuttle astronauts appears to be significantly less than their estimated energy expenditure. This could adversely affect anabolic processes integral to bone remodeling, as well as net acid excretion and calcium balance. Sodium intake in astronauts has been reported to be well above that recommended to moderate urinary calcium excretion. This amount might also adversely affect humoral vascular responsiveness to salt and water loading in astronauts prior to return to Earth. Calcium intake, on the other hand, appears to be very close to the recommended daily intake, and it should not require major modification. It might be useful to calculate dietary cation-anion balance for comparison to urinary pH and titratable acid excretion in order to determine potential effects of supplemental dietary alkalization on net acid excretion and calcium balance. While changes in blood gas parameters have not been observed in the limited studies to date, increased urinary calcium and sulfate losses may reflect increases in net acid excretion which could be moderated by dietary alkalization.

Few data are available that define the mechanisms associated with the changes in mineral mass/bone loss/calcium homeostasis during spaceflight. Data are required to determine if dietary sodium restriction or dietary alkalization might be effective. Also, preflight conditioning and changes in skeletal loading levels preflight might be helpful. If diet and preflight conditioning are not effective in minimizing the changes in bone/calcium/connective tissue, then drug therapy might be implemented. However, most drugs that are effective in inhibiting bone resorption are incorporated into the bone mineral and may have long-lasting effects. It may be preferable to maintain musculoskeletal mass and integrity as a system rather than provide countermeasures effective for only muscle or only bone. The musculoskeletal changes must be minimized if crewmembers are to be able to function effectively upon return to Earth or when they land on other planets.

IV. Recommendations

- 1) NASA needs to review its current dietary protocols, considering diets that minimize calcium and nitrogen loss. Specific recommendations are delineated in Appendix C.
- 2) Preflight conditioning and appropriate onboard exercises are recommended and would be similar to those recommended in the Skeletal Muscle Discipline section.
- 3) Drugs should be evaluated if the physiological countermeasures recommended above are ineffective; most available drugs have unwanted side effects and their efficacy against bone loss during space flight is not established. Certain drugs, particularly those known to increase bone formation, e.g. intermittent

PTH, and/or inhibitors of bone resorption, e.g. bisphosphonates, could be evaluated for efficacy in preventing space flight induced osteopenia. .

4) NASA should investigate practical strategies for creating artificial gravity as a means to counteract bone loss.

5) Long term goals of NASA, in conjunction with the Exercise Countermeasures Program and Nutrition Program at JSC, need to focus studies toward basic and applied research that identifies the mechanisms of urinary calcium elevation, endocrine changes, bone loss, and connective tissue changes associated with spaceflight and to seek more effective countermeasures for preserving mineral mass, bone strength, and connective tissue integrity. These studies should consider interactions of physical activity, diet, fluid shifts, pharmacological, and other factors to understand these changes.

V. Overarching issues

Nutrition and exercise that integrates activities supporting cardiovascular, vestibular and neuromotor, and musculoskeletal homeostasis were issues raised by most disciplines. In addition, the countermeasures selected should be based on crew compliance and health issues.

Cardiovascular Function Discipline Report on Countermeasures

I. Nature of the Problem

Evidence from spaceflight missions and ground based analog experiments indicates that prolonged exposure to microgravity induces a variety of adaptations in the function of the cardiovascular system that significantly compromise orthostatic tolerance and physical work performance upon return to earth's 1G environment. Reduced orthostatic and work capacities are associated with alterations in cardiac and vascular functions that appear to include the following characteristics:

- 1) Significant reductions in circulating blood volume as a result of a rapid decrease in plasma volume followed by a more gradual loss of red blood cell mass.
- 2) Reductions in stroke volume and cardiac output with little evidence of compromise in normal ventricular function.
- 3) Possible increased occurrence of cardiac arrhythmias.
- 4) Alterations in peripheral vascular function that include increased venous compliance of the lower extremities, reduced muscle blood flow, and limited capacity for increasing peripheral resistance in response to standing on return to 1-g.
- 5) Changes in autonomic nervous system function, including both afferent and efferent limbs of reflexes.

- 6) Altered baroreflex function that is associated with attenuated tachycardia and decreased vasoconstrictive response to hypotensive stimuli.
- 7) Possible reduction in cardiac mass.
- 8) Reduction in central venous pressure, as compared to head-down posture pre-launch in 1-g.

Together, the above listed adaptations in cardiovascular function may result from underlying mechanisms that contribute to the well-documented profile of orthostatic intolerance and lower aerobic capacity following spaceflight. Combinations of these functional deficits has the potential to deleteriously affect an astronaut's ability to egress the space vehicle following reentry in the case of an emergency situation upon landing.

II. Countermeasures to the Problem

The development of a countermeasure program designed to maintain normal cardiovascular function should continue to focus on two primary operational functions and include the following approaches:

- 1) Protection of orthostatic tolerance
 - a. Countermeasures in use include:
 - a.1. Astronauts consume an isotonic saline 'load' consisting of 8 salt tablets (1 g NaCl per tablet) with about 960 ml fluid approximately 2 hours before re-entry in an attempt to restore plasma and blood volume.
 - a.2. Use of an anti-G suit inflated to approximately 1 psi during re-entry and landing that provides protection against blood pooling in the lower extremities. (The standard Air Force CSU-13B/P anti-G suit is currently used during landing).
 - a.3. A specially-designed full coverage Liquid Cooling Garment (LCG) with a network of plastic tubing that allows for the circulation of water across the body surface is worn under the Landing and Reentry Suit (LES) to provide conductive cooling of the astronaut in an effort to minimize the peripheral vasodilatory effect of body heating and improve comfort.
 - a.4. A reconfiguration of the seats in the middeck of the Space Shuttle allows astronauts to lie on their backs in an attempt to minimize the +Gz orthostatic impact on the cardiovascular system of crewmembers during reentry from orbit, after long-duration space flight on Mir and, in the future, on the International Space Station.
 - b. Countermeasures that have been attempted in flight and are no longer being pursued, but could be, if new evidence indicates they have promise:
 - b.1. Exposing astronauts to 4 hours of lower body negative pressure (LBNP) at 30mmHg decompression with consumption of the standard oral fluid load during the early part of the exposure. This LBNP/Saline 'Soak' is performed 24 hours before landing.

b.2. A single-bladder Re-entry Anti-G Suit (REAGS) that provides protection against blood pooling in the lower extremities without covering the abdominal area, knees, or the buttock, inflated to approximately 1 psi during re-entry.

b.3. An acute graded cycle exercise protocol designed to elicit maximal effort (maximal oxygen uptake) performed within 24 hours of reentry from orbit which might restore blood volume, autonomic function, and orthostatic tolerance.

c. Potential countermeasures that have not been tried include:

c.1. Resistive exercise designed to prevent muscle atrophy might minimize blood pooling in the lower extremities during standing. Also, reflexes associated with autonomic regulation of blood pressure could be maintained or protected by resistive exercise designed to defend normal motor unit recruitment.

c.2. Periodic exercise during flight within a lower-body negative pressure (LBNP) device might maintain orthostatic function as well as aerobic capacity.

c.3. The use of various pharmacological countermeasures, such as adrenergic agonists and antagonists might prove effective in enhancement of autonomic responses to orthostatic challenges postflight.

c.4. The use of a small-arm centrifuge (artificial gravity) might replace the physiological stimuli to the cardiovascular system naturally provided in earth's environment, and forces greater than 1G might be used to minimize the time required for countermeasure application.

c.5. Since variations in fluid-electrolyte balance (e.g., hyponatremia, potassium deficiency) can impact cardiovascular function, the application of standards for dietary intake during spaceflight could prove to be an important nutrition countermeasure.

c.6. Periodic application of negative pressure to the carotid baroreceptors with the use of a neck pressure chamber might provide a pressure loading stimulus in an attempt to maintain normal baroreflex control of cardiac function (Note: this is speculative and unlikely to be acceptable).

2) Protection of aerobic capacity

a) Dynamic physical exercise of moderate intensity and long duration designed to provide endurance profiles has been performed during spaceflight using cycle ergometer, rower, and treadmill devices. No set prescription has yet been determined; hence, currently, the amount of exercise (frequency, duration, intensity) is variable.

b) An elasticized garment (Penguin Suit) with rubber bands woven into the fabric, extending from the shoulders to the waist and from the waist to the lower extremities, provides continuous tension (exercise) for antigravity muscles. The benefit derived from its application has not been systematically evaluated.

- c) A Human-Powered Centrifuge is a potential countermeasure designed to simultaneously apply cycle exercise (endurance) with head-to-foot gravity (+Gz) acceleration by using a short-arm (<3 m), dual cycle, human-powered centrifuge. The induced acceleration may potentiate the beneficial effects of exercise and other countermeasures on cardiovascular function after return from spaceflight.
- d) Exercise within an LBNP device (See 1.c.2., above).

III. Concerns

The use of ground-based analogs for the study of long-term exposure to microgravity and its effects on the human cardiovascular system is justified by numerous similarities in the physiological adaptations caused by both actual and simulated microgravity. However, numerous dissimilarities that were presented in our discussions raised the concern that ground-based models may not be adequate and perhaps some microgravity effects cannot be studied on the ground. Unfortunately, a significant use of pharmacological agents and lack of control over experimental conditions such as sleeping, eating (nutrition) and scheduled mission activities significantly limits our ability to interpret how much of the observed differences between spaceflight and ground-based experiments is actually the result of the environments and how much is due to these numerous confounding factors.

The identification and use of tests designed to monitor the effectiveness of a countermeasure are critical to the success of any countermeasure program. Many pre- and post-flight tests are developed as a result of constraints in mission schedules and medical operations. There is concern that some tests such as the 10-minute stand test or submaximal exercise used for cardiovascular assessment do not have sensitivity great enough to measure the effectiveness of the countermeasures being tested.

The observations from SLS-1 and SLS-2 that peak VO₂ in spaceflight was not reduced from pre-flight values, but was reduced by 22% upon return to Earth, raises concern regarding the ability to predict effectiveness of cardiovascular countermeasures with measurements made during spaceflight.

There is compelling evidence that the vestibular system has pronounced influence through the central nervous system on autonomic control of cardiovascular reflex mechanisms associated with blood pressure regulation. It is our recommendation that expertise be recruited to examine potential countermeasures for vestibular dysfunctions that may contribute to the treatment of compromised orthostatic tolerance post flight.

IV. Recommendations

- 1) A basic approach to assure a countermeasure program that will enhance 'health' and function during long-duration spaceflight should include several actions that are associated with data collection and medical monitoring of the cardiovascular system. These activities should include, but not be limited to:
 - a. Cardiac rate and rhythm monitoring should be done in an optimal manner during flight, e.g., one day biweekly, with periodic downlinkage.
 - b. Testing suits, like the penguin suit, with detection and recording of exogenous loads they provide.
 - c. Collecting data to assess any relationships between microgravity exposure, the use of physical countermeasures and drugs, and the frequency and severity of arrhythmias.

- d. Using data to correlate external physical loads from countermeasure devices (e.g., penguin suit, resistive exercise devices, cycle ergometer, etc.) with inflight and post-flight cardiovascular performance (e.g., aerobic capacity, orthostatic tolerance, autonomic function).
- e. Observing cardiovascular structure and performance in-flight, if technology becomes available, and immediately post-flight.
- f. Initiating a program for testing, and determining pharmacokinetics and pharmacodynamics of pharmacologic agents likely to benefit cardiovascular function.
- g. Defining the relation between diet and metabolic balance data previously obtained in microgravity; from diet logs, relate dietary intake to cardiovascular performance and rhythm.

2) Continue research to identify the optimal exercise prescription(s) (i.e., minimal amount of exercise intensity, duration, frequency, and mode) required to produce the greatest cardiovascular benefits associated with physical and orthostatic functions. Also, there is a need to identify at what point in the mission exercise countermeasures should be applied. Continued ground research to evaluate and validate exercise countermeasure protocols should be conducted prior to space flight.

3) Research is needed to identify countermeasure procedures that will acutely increase central venous pressure operational setpoint and plasma albumin. Fluid loading should be combined with such countermeasure techniques. (Acute exercise designed to elicit maximal aerobic effort restored plasma volume in bedrest subjects; the combination of fluid loading and acute maximal exercise may be effective to enhance restoration of vascular volume).

4) The use of inflight exercise within the LBNP chamber as a countermeasure should be examined. While members of the Committee questioned its relevance for supporting orthostatic tolerance, the fact that this technique does support aerobic capacity indicates additional research should be done to further define its possible use for improving cardiovascular homeostasis.

5) NASA should continue to develop the Liquid Cooling Garment (LCG) as a countermeasure, but continue development and testing of an upper torso LCG designed with greater cooling tube density to provide adequate total cooling capacity.

6) NASA should continue to develop an anti-G suit that can be comfortably inflated and worn in combination with the LCG to provide maximum protection against orthostatic compromise during re-entry and landing.

7) There are numerous approaches that have not been specifically tested in the U.S. space program, but hold potential as countermeasures that NASA should consider. These include the 'Penguin' suit, resistive exercise, pharmacological agents, and a human-powered centrifuge. These 'potential' countermeasures may be worthy of support for future ground and spaceflight experiments in order to investigate and define their impact on cardiovascular functions.

8) The LBNP/Saline "Soak" procedure has not proven effective in ameliorating cardiovascular stress during post-flight stand tests and should therefore be discontinued as a countermeasure. However, use of LBNP for evaluation of other cardiovascular countermeasures and functions during a space mission should continue.

V. Overarching Issues

One goal of countermeasure programs for maintaining astronaut health and fitness during long duration spaceflight is to assure that each crew person has sufficient power, strength, and endurance to conduct daily tasks and sufficient reserve and functional capacity to perform emergency functions. To accomplish this, a strong scientific base will be required, as well as careful operational validation and testing. An understanding of the basic physiology of spaceflight and mechanisms involved in adaptation to microgravity is needed to provide the most efficient and effective countermeasures. This important knowledge will require a scientific approach and not a trial-and-error approach. The development of a systematic approach to investigation of the effects of long duration exposure to spaceflight on the cardiovascular system will include the integration of three basic issues: 1) identification and quantification of physiological adaptations; 2) determination of underlying mechanisms; and 3) identification of the physiological stimulus required to maintain normal function in 1G (on earth). Once basic research investigations have identified the physiological stimulus required to maintain normal function in 1G (on earth), operational research can be directed to testing the application of 'treatments' that provide similar stimuli to the cardiovascular system and assess their effectiveness on orthostatic and exercise performance.

The success of this approach will depend upon an organization that can oversee and coordinate the numerous issues and subsequent investigations to assure optimal integration of all activities and knowledge.

Use of exercise as an effective countermeasure will depend on a thorough understanding of operant mechanisms of physiological adaptation to microgravity and how they are affected by the stimulus of specific intensities, durations, frequencies, and modes of exercise and other treatments that have yet to be clearly defined. Present practices appear to be excessively costly in terms of both time and money. Better countermeasure should be identified and tested on the ground and during spaceflight. Data from both ground and inflight investigations have suggested several findings and strategies that can be used for development of exercise and other countermeasures for training before, during, and after spaceflight:

1. It is clear that no one current countermeasure applied during exposure to microgravity has been completely successful in maintaining or restoring impaired cardiovascular function. Research on the development of countermeasures for cardiovascular (and other physiological) functions should include tests for combinations of countermeasure prescriptions.
2. Ground-based models should be used to develop information and understanding of basic mechanisms that underlie deleterious physiological adaptation to microgravity. Head-down tilt bedrest is one model that has been used effectively investigate some of the alterations in physiological functions induced by exposure of crews to microgravity. This model provides a controlled laboratory environment to conduct experiments for later inflight testing.
3. In addition to exercise alone, some degree of gravity loading with acceleration may be required to provide optimum effects.
4. Future inflight exercise-training programs will probably require a mix of dynamic and resistance modes to maintain both anatomical structure and physiological function. Each of these modes of exercise with varying profiles of intensity, frequency and duration provide specific stimuli to the cardiovascular system. For optimum countermeasure effects, it is important to determine which types of exercise provide beneficial as opposed to detrimental alterations in cardiovascular function

Development of flight countermeasure prescriptions must include consideration of equipment that meets feasible and effective operational requirements. The equipment must be convenient to use so it will promote optimum crewmember compliance. Devices should be small; easy to handle, setup, and stow; and function with minimal external power requirement.

Finally, research efforts should help in the identification of minimal countermeasure application (e.g., time, workload, etc.) required for maintaining health, safety and productivity of crewmembers¹. This approach can be successful only if specific criteria are well defined through systematic analysis of the physical and physiological requirements for adequate accomplishment of flight-operational tasks.

Clinical Subgroup Report on Countermeasures

I. Nature of the Problem

The International Space Station (ISS) will be used to define the life sciences needs for both long stays in low earth orbit (LEO), and exploration class missions (including Moon and Mars missions). By use of the ISS facilities and crew, NASA will achieve an incremental gain in data and knowledge which will be reviewed and revised on a periodic basis. There is a large overlap in knowledge required for safe execution of long term LEO missions and exploration missions. Some exploration requirements are unique and will require unique investigations and highly specific countermeasures and health monitoring.

For long term flights, the very important issues of radiation exposure, psychosocial adaptation, extravehicular performance, and routine and emergency medical care need to be considered, and they are currently being considered by other groups within NASA.

II. Countermeasures to the Problem

Countermeasures in the space shuttle and space station programs impacting clinical medical issues are summarized in Table 1. The majority of the issues delineated are described in a general context, since most of these countermeasure activities, (e.g., exercise) are described in considerable detail in the other discipline reports.

III. Concerns:

The clinical subgroup of the task force found that some basic background and descriptive work in problem definition was lacking. While the research community has focused on slices of the problems, a more all encompassing, clinical approach has not been employed.

TABLE 1

¹ Prolonged daily exercise presently used during spaceflight is costly and drains life support materials which are expensive to place and maintain in orbit. For instance, the average daily exercise metabolic cost of 725 kcal during Russian missions represent about 25% of the total caloric intake of 3,150 kcal. If exercise time and ensuing energy costs could be halved, the saving over a 6-month mission would be enough to supply another crewperson with an additional 27 days of food, 23 days of water, and 13 days of oxygen. This issue will become more critical on longer interplanetary missions.

	ACCEPTED	POTENTIAL
Preflight	*Health Stabilization Program	*Conditioning program
	*Circadian shifting	*Psychological support
	*Schedule adjustment	*Nutritional guidance and support
	*Medical training/education	
	*Drug sensitivity testing	
	*Selection physical	
	*Flight certification	
In-flight		
Psychosocial	*Sleep/rest/schedule adjustment	*Conditioning program
	*Exercise	*Psychosocial support
		*Medications
Space Adaptation Syndrome	*oral and IM Phenergan	*Preadaptation
	*Private Medical Conference	
	*Good hydration	
	*Schedule adjustment	
Bone Loss		*Medications
		*Exercise
Aerobic Capacity	*Exercise	
Muscle Loss		*Exercise
General Health	*Balanced diet, vitamins	
Entry/Landing Syndrome	*Anti-G suit	*Medications
	*Cooling Garment	*In-flight exercise
	*Fluid loading	
	*Recumbent Seats	
Post-flight	*Rehabilitation (long duration)	*Rehabilitation
		*Conditioning Program

IV. Recommendations:

1. A critical review of all laboratory work-up data and medical reports performed on a routine basis during the Space Shuttle program must be undertaken. This review should include studies done as part of the selection, annual physical, and flight-related medical exams. This review should help determine those studies that will be necessary to make real time decisions and to practice preventive medicine on all flights regardless of duration. This review of historical clinical data also can be used to assess which laboratory studies should be monitored on a regular basis and the outcomes may provide information to highlight previously unidentified potential problems.
2. The problems associated with re-entry and landing, i.e., "Re-entry and Landing Syndrome", need to be carefully described through a review of medical records and existing performance data as well as via collection of prospective data. This description should include the full symptom complex, incidence, time course and treatments. It is expected that this Syndrome cuts across the cardiovascular, neuro-vestibular and musculoskeletal disciplines. In addition, any real problems which have occurred as a result of this syndrome should be catalogued. The 'requirements' for performance of crew egress, in a normal and emergency situation, should be defined and accepted by NASA program management.
3. The Countermeasure Research Plan should be developed in a manner that integrates all research disciplines to get the most efficient system of countermeasures possible. For example, a countermeasure could be developed such that its effectiveness cuts across disciplines, and addresses two or three (or more) physiologic systems. It is essential that the medical operations staff work closely with the research team(s) to ensure a clinical and operational focus to the countermeasure integrated plan. The medical operations team could also provide input to ensure that the research and subsequent countermeasure(s) are compatible with the spacecraft environment and crew schedule so that the countermeasure program will yield maximum crew cooperation and compliance.

Neurological Task Force Report on Countermeasures

Neurological issues were addressed by the Vestibular Countermeasures Task Group which was formed to provide a report to the Task Force on Countermeasures about the current understanding of neurologic adaptation to space flight and return to earth, and the development and implementation of countermeasures to lessen or alleviate adverse effects.

I. Nature of the Problem:

The Task Group determined the nature and scope of the problems associated with neurological adaptation to space flight, based on the available data. "Vestibular problems" for space flight have not disappeared with the introduction of promethazine injections to treat acute episodes of space motion sickness early after entry into weightlessness. Observations continue to suggest that several important problems remain affecting astronaut health and safety for short and long duration space flight.

A number of specific, measurable sensorimotor alterations have been identified that occur due to space flight. These include the following:

- 1) There are alterations in eye-head coordination, including changes in horizontal, vertical and linear VOR function, and combined eye-head smooth pursuit target tracking
- 2) Decrements occur in postural equilibrium control and locomotion, including disruption in vestibular contribution to postural control changes in head-trunk coordination.
- 3) Sensory illusions occur such that the perception of head tilt is reinterpreted as translation (otolith tilt translation phenomenon), and phase lag, gain and directional illusions may occur.
- 4) Changes in spatial orientation ability occur.
- 5) State transition problems occur. For example, during readaptation to a 1-g environment the recovered adaptive state is fragile and instantaneous state transitions can occur between 0-g and 1-g adaptive states, leading to sudden motor control dysfunction.
- 6) There are changes in proprioceptive function, related primarily to passive localization.
- 7) Modification in vestibulospinal reflex function occurs.
- 8) Optokinetic reflex function is transiently impaired.
- 9) Increased visual dependency occurs following transitions to and from microgravity.
- 10) Anatomical vestibular end organ changes occur in experimental animals.
- 11) Space motion sickness occurs in the first few days of flight.

II. Concerns:

Problems associated with multi-sensory and multi-system interactions (e.g., otolith-cardio linkage) and integration exist. Also, attempts to maintain or improve performance of a physiological system may cause or exacerbate problems in other physiological systems. As a result, there may be operational problems due to sensorimotor alterations. These include:

- 1) Control of Shuttle Landing: alterations in eye-head coordination and sensory illusions might be thought to lead to difficulties in reading flight instruments, checklists, interpreting ground-based landing aides, estimation of altitude, and making gaze transitions between inside and outside the flight deck. However, analysis of pilot landing performance on all shuttle flights to date fails to identify any correlation between mission duration and accuracy of landing speed, position, or touchdown velocity. This finding does not preclude the possibility of problems associated with higher workload or difficulty in overcoming illusions. The situation bears further monitoring, including post-flight debriefs aimed at identifying such problems.
- 2) Unaided Egress: decrements in postural and locomotor control, as well as motion sickness, may lead to impaired egress ability including difficulty in leaving the seat (getting out of restraints), moving to the hatch, and moving away from the Orbiter in an emergency or in setting up habitats and shelters on a distant planet.

3) Extravehicular Activity(EVA): Sensory illusions during EVA may cause crew members to become disoriented. Sensory illusions could also cause crew members to provide incorrect directions to RMS operators during joint EVA-RMS operations.

4) Space Motion Sickness (SMS): This problem leads to decreased efficiency early in flight, and could cause some difficulties during re-entry and immediately after landing.

III. Countermeasures to the Problem and Associated Recommendations:

Ideally, countermeasures to any problem should undergo an evolution including: a) basic science rationale and laboratory research; b) efficacy research/clinical evaluation; c) cost effectiveness evaluation; risk/benefit evaluation; d) operational effectiveness; e) assessment of potential interference with other countermeasures or shuttle operations; f) acceptance (with continuing “fine-tuning” as new data become available). In the context of these issues the underlying assumption is that the evaluation of the efficacy of countermeasures should focus on the functional link between sensorimotor alterations and real operational deficits (e.g. changes in eye-head coordination and dynamic visual acuity).

The Task Group evaluated the existing countermeasures for neurological perturbations caused by space flight. The neurosensory problems addressed by existing countermeasures include: 1) space motion sickness (SMS), which occurs primarily during the initial days of a space mission; 2) disturbances associated with an ill-defined but operationally important "entry/landing syndrome"; and 3) more severe and varied disturbances following long-duration (+2 months) microgravity exposure. The Task Group determined that the existing countermeasures aimed at these conditions can be divided into 2 categories:

Category 1 countermeasures are designated as tried, "proven" (in the U.S. program) currently-accepted and used procedures. Category 2 countermeasures include those procedures that are used informally and essentially based on personal communication among astronauts, as well as between astronauts and flight surgeons. These procedures also include those for which apparatus and procedures have been developed, but for which ground research is incomplete and/or efficacy has not been established. (Table 1 presents the two categories of existing countermeasures aimed at the three conditions. Charts presenting detailed information about each countermeasure and providing a recommendation associated with its use can be found in Appendix E).

Recommendations For Early-inflight SMS:

Recommendations for Category 1 countermeasures include: 1) continue and improve crew training, briefing, and timeline adjustment based on current best-available information; 2) further evaluation of promethazine route of administration, inflight side-effects and development of alternative drug interventions that are closer to 100% effective; 3) development of predictors to identify individuals who

Table 1: EXISTING NEUROLOGICAL COUNTERMEASURES

	CATEGORY 1	CATEGORY 2
	Tried, “Proven”, Accepted and Used	Developed, Protocols in place but not implemented, Anecdotal
Early Shuttle Missions SMS	<ol style="list-style-type: none"> 1. Oral & Promethazine Injections 2. Crew Training / Briefings 3. Timeline Adjustments 	<ol style="list-style-type: none"> 1. PAT: TTD/DOME 2. WETF Experience 3. Training in unusual attitude environments
Shuttle Landing Phase “Landing Syndrome”	<ol style="list-style-type: none"> 4. Crew Training / Briefings 5. Recency of training 6. Operational Recommendations 7. In-flight Exercise 	<ol style="list-style-type: none"> 4. Medications during/after entry and landing 5. PILOT¹ simulator 6. Performing head movements during entry 7. Crew Assisted Egress 8. Preflight Adaptation Training (PAT)
Long Duration Missions	<ol style="list-style-type: none"> 8. Assisted Egress 	

¹ Portable Inflight Landing Operations Trainer

might benefit from additional or alternative interventions; 4) and development of coping procedures for the few individuals who fail to adapt for prolonged periods.

Recommendations for Category 2 countermeasures include: 1) evaluation of the efficacy of the proposed SMS-alleviation procedure using the Preflight Adaptation Training (PAT) devices, and 2) increase unusual attitude experience base, especially SCUBA experience, and use of WETF and DOME PAT for familiarization with the shuttle in unusual attitudes.

Recommendations Concerning Entry/Landing Disturbances:

Recommendations for Category 1 countermeasures include: (1) continue and improve crew briefings based on best available information, (2) continue to provide adequate training close to flight, and inflight (3) continue to modify operational landing requirements to create best "vestibular" environment, and (4) define best exercise protocols to prevent anti-gravity muscle loss.

Recommendations for Category 2 countermeasures include: (1) continue and refine crew briefing on risks / benefits of head movements during entry and immediately post landing, (2) evaluate entry / post-landing head movements, as compared to no head movements, and develop an appropriate protocol, (3) continue to use, improve and evaluate inflight landing task simulators, (4) egress training should include scenarios for assisting ill crew members, (5) meclizine / phenegran treatment should be evaluated and (6) efficacy of the PAT devices using the dual-adaptation protocol should be assessed.

Recommendations Concerning Entry/Landing Disturbances After Long-duration (2+ months) Missions:

For problems following long-duration missions, the only accepted countermeasure is assisted egress.

Generic Recommendations:

The Task Group also generated the following additional generic recommendations that should be addressed:

- 1) Contributions of fluid loading to postflight vomiting should be assessed.
- 2) An objective scale in order to quantify possible relationships among in-flight exercise, pre-flight rotation tolerance, and post-landing postural control should be developed.
- 3) A possible neurosensory down-side to recumbency during entry should be addressed.
- 4) Data from crew debriefs should be quantified and published to facilitate countermeasure development

Future Countermeasure Strategies

The Task Group identified several potential countermeasures which could be effective in counteracting the vestibular-sensorimotor affects of space flight. Below is a summary of these potential countermeasures for the three key stages of a mission: 1) the transition to orbit; 2) on orbit; and 3) the landing stages of a mission. Findings and recommendations are provided. Detailed reports on the identified countermeasures are presented in Appendix E.

Transition To Orbit:

Train crew to adapt head movement strategies that minimize SMS and thus avoid medications. Base these upon predictive tests that identify individual propensities, provocative movements.

Consideration should be given to designing an ultralight, miniaturized head movement monitoring system for training and dynamic restraint. (See Head Movement Monitoring/Dynamic Restraint/Training Systems in Appendix E)

Development of ground-based programs designed to train crew members to orient and navigate in 3 dimensions, including techniques for them to learn to recognize objects and spacecraft interiors from arbitrary ("agravic") body orientations, should be considered. Examples include various VR based approaches, e.g. PAT and more portable head mounted VE systems, neutral buoyancy EVA training facilities, e.g. WETF, and reorientable simulator modules for both shuttle and station, and parabolic flight aircraft .

On Orbit

There is considerable experimental evidence that the prediction of sensorimotor patterns by the brain plays a central role in control of posture, eye movements and equilibrium. It is therefore likely that with appropriate training astronauts could learn to maintain two neuro-vestibular adaptive states--one appropriate for the terrestrial environment, one appropriate for a microgravity environment.

Specifically, the group recommends that procedures and equipment be provided on orbit that allow astronauts to practice moving their heads or bodies under conditions that approximate those on earth. The goal is to allow them to maintain the terrestrial adapted state on orbit thereby minimizing problems during landing and egress. Two protocols are recommended:

1) The maintenance of the capacity of the vestibular system to function in a terrestrial environment could be accomplished with a centrifuge facility that allows the crew to make active head movements in a 1 g field on orbit while minimizing or avoiding Coriolis and cross-coupling. An ideal configuration would allow pitch and roll head movements in a body vertical (g_z) centrifugal field. This would require a large radius, human rated centrifuge. It is possible that at least partial benefits could be obtained with a smaller centrifuge. Ground-based research is required to investigate options.

2) The use of a modified treadmill system is recommended to maintain posture and kinematic strategies formed by proprioceptive and visual cues that are appropriate for 1g. The recent progress in vibrotactile devices for orientation and motion feedback should be reviewed and suitable countermeasure proposals based on these findings should be developed. (See Appendix E)

Landing

Induce dual adaptation to both 1-g and 0-g environments using a 4 meter radius centrifuge. This device could preserve appropriate predictive processing of vestibular signals in 1g and would allow the active head and possibly body movements required to develop dual adaptation on orbit.

Maintain musculoskeletal (proprioceptive, kinematic) postural strategies via a special purpose treadmill designed to allow linked inverted pendulum movements for reproduction of terrestrial postural control including pitch plane body kinematics.

Development of a quick-release equipment system to aid egress should be considered.

IV Overarching issues

The Task Group identified two overarching issues related to neurological adaptation to space flight and countermeasures aimed at addressing them.

Issue 1: The problems are crewmember specific, depending on their role in the flight (Space Station and Exploration Scenario).

There are three categories of affected crew members:

- 1) Long-Term On-Board Scientist: This crew member's duties involve performing inflight experimental procedures. The potential risks experienced by this individual include: a) difficulties performing emergency egress; and b) long-term or potentially permanent changes in sensorimotor function
- 2) Long-Term Operator: This crew member is responsible for Station operation (EVA, RMS etc.) or planetary exploration and could be responsible for performing a contingency Soyuz return from the International Space Station; but nominally would be returning with no operational duties. The potential risks experienced by this individual include: a) difficulties performing non-Earth planetary and/or emergency egress; b) long-term or potentially permanent changes in sensorimotor functions; d) problems with station operation, including EVA, RMS, contingency procedures; e) spacecraft operational difficulties during contingency return.
- 3) Short-Term Operator: These crew members arrive on Shuttle and are docked to the Station for a 1 to 2 week duration. Their responsibilities include ferrying the long-term crew members back to Earth and performing Shuttle/Station operations. The potential risks experienced by this individual include: SMS; difficulties performing emergency egress; and shuttle operations (rendezvous, EVA, RMS, and re-entry).

It is recommended that countermeasures should be tailored to crew member's duty.

Issue 2: There exists a large body of relevant data that have not been analyzed. These include: a) data from STS flights that are not readily available. Additionally, physiological data have not been correlated with operational performance measures (e.g., Do short landings correlate with the commander's report of sensory illusions ?); b) a substantial Russian experience with long-duration flight that is not readily available.

It is recommended that future efforts should include collation, review, and evaluation of existing extensive operational and experimental databases. The operational databases (e.g., medical records, STA databases) would need to be analyzed by appropriate persons (e.g., flight surgeons, aircraft operations, respectively) to group the data and eliminate individual attributions and retain compliance with Privacy Act provisions.

Behavior and Performance Discipline Report on Countermeasures

I. Nature of the Problem

Before specific countermeasures can be proposed, developed and tested, specific spaceflight, ground support, crew, and associated family problems in Behavior and Performance (BP) need to be defined and quantified. NASA has begun this process by initiating the Behavior and Performance Working Group (BPWG).

Behavior and performance issues become increasingly more important as space missions become longer, and space flight teams become larger and more heterogeneous. The isolated and unique environment of space and space vehicles present crews with additional stresses above and beyond that which are normally encountered in training. Extended duration missions will place a greater stress on individuals, interpersonal and group relations for astronaut crews, between astronaut crews and ground control, and on astronaut families.

The BPWG believes that the first two recommendations listed below should be given the highest priority. The third should be planned and conducted as soon as possible, but should build on the current knowledge and experience base within NASA. Research activities which directly involve astronauts should be based upon the experience and knowledge of the issues particular to this unique mission environment, and require good personal rapport and trust with the subjects. There are both intramural and extramural scientists nationally, as well as international space agency based or external scientists, that meet these requirements.

II. Countermeasures to the problem

Current countermeasures focus primarily on the individual, mission crew, and to some extent the families of mission crews. Some work has been done to address: the overall mission and ground crew as a team, cultural issues for the mission and ground crews, and families of ground crews and the larger cultural and overall team aspects of space missions. Current countermeasures are part of an organized psychological and training program addressing the full spectrum of requirements from selection through post-flight readaptation. No quantitative validation of these measures has been made to date.

Selection criteria focus on:

Select Out - based on medical criteria

Select- In - based on non-medical criteria (job proficiencies, mission drivers).

Astronauts receive training in cross-cultural issues; information regarding what is known about psychological factors in extended space flight; lessons from Analog Environments; leadership and team functioning; crew resource management; and clinical resources for astronauts.

Preflight support for overseas assignments include two-way video visits on weekly basis with family stateside; video library; journal/newspaper subscriptions; daily electronic news; advocacy (Moscow rest

and recreation base, including some sports equipment); site visits; e-mail; and pre-deployment lunches with families.

Inflight support for overseas assignments include packages delivered to MIR on a regular basis; audio and video family conferences; e-mail; ham radio; audio and video US news, sports, events; special conferences on holidays (e.g. Birthdays, Mother's Day); personal diversions (e.g. special cassettes, books, CD ROM, videos, family album, audio messages); and continuing psychological support services to family members of astronaut mission crews.

Monitoring of the astronauts includes a questionnaire on mood sleep and stress, and countermeasure usage and effectiveness; weekly family tag ups; private medical conferences; daily reports from ground crew; private psychological conferences (planned for Space Station); and Russian psychological group reports.

Postflight support includes debriefs of astronauts alone and with family; daily contact during physical rehabilitation; and daily medical review.

III. Concerns:

Substantial data may be available in the area of behavior and performance from environments analogous to space flight. International experiences, as well as information gathered on the US Space Program, need to be fully analyzed.

IV. Recommendations:

It is the consensus of the BPWG that the highest priority activities are:

1. Critical Review of Analog Studies - There is a great deal of literature from many isolated and unique 'analog' environments. A comprehensive, systematic review of these studies undertaken with the viewpoint of their true analogy with space flight would clarify the usefulness of these studies to NASA, and may present a more integrated and complete picture of life in isolated environments. After this project is completed, remaining areas of research that should be undertaken in analog environments should be identified. Analog studies that are felt to have a high correlation with space flight should be used to define information that is particularly pertinent to small teams operating in harsh environments. Examples of information that would be very useful to operational space flight include: the identification of psychological factors of good performers; the natural history of psychological adaptation to harsh environments; the identification of types of problems that arise during deployments; the outcomes of attempted interventions and preventative measures - - all of which should include the issue of balance between crew autonomy and integration with ground support teams.

2. Review of the Russian Experience - Nearly all the world's experience in long term space flight is resident in the Russian space program. A comprehensive review of the Russian data and observations in the field of behavior and performance should be undertaken and a written summary should be produced. This should include initial selection and pre-flight selection processes, preflight psychological evaluation, training and support, and in-flight evaluation (monitoring) and support activities, and post-flight monitoring and interventions. The importance of this information is based upon the fact that it is derived from real events in the space flight environment. This activity would enable NASA to conduct a

research program at a higher level of understanding and knowledge. A systematic look at Russian selection procedures, training, flight experience and related issues may offer transferable areas of expertise.

3. Astronaut Selection and Crew Composition - Psychologically healthy individuals and well-functioning crews are critical to mission success. One would like to be assured of selecting psychologically healthy individuals well-suited for the unique duties and stresses of this job. Additional efforts should be made to follow-up on the 1990 study by Rose and Helmreich which looked at using objective, validated personality measures to psychologically screen astronaut applicants as part of the initial selection process. An emphasis should be placed upon factors related to long term space flight missions, of greater than 30 days. After this, research that improves our ability to assemble optimal crews - - not just as individuals, but also as a whole unit - - would be valuable. Related to this, research should be solicited regarding the best methods and protocols for training individuals and whole crews prior to flight on topics such as conflict management and resolution, communication skill enhancement, cross cultural training, team maintenance, and stress management.

4. Other - A research program that addresses the specific area of countermeasures through a three part program of:

1. retrospective analysis of previous space missions and appropriate analogs,
2. ongoing analysis of current space and analog activities including Shuttle, MIR, and appropriate analogs and simulations and
3. future research on a range of applied and basic areas of behavior and performance.

And a process that addresses:

1. the space mission team, ground support team and space mission crew families
2. preflight, flight and postflight time periods
3. technology design processes.
4. participation with other federal agencies
5. participation with international partners
6. maintaining the BPWG and expand its scope to fully address age, gender, culture, group dynamics.

In addition, many different areas related to the field of behavior and performance would benefit from further research. The committee also recognizes that resources are limited, and not all studies can be done. The group does, however, recommend that research in the area of behavior and performance be actively pursued. Appendix F of this report contains greater detail on the areas of research recommended for consideration with respect to countermeasures. The three general areas of research recommended are:

- psychiatric issues
- individual/personal psychological development:
- group (dyad, team, culture) psychological development:

V. Overarching Issues and Recommendations

Potential future countermeasures touched on by the BPWG specifically focused on the need to have a balanced BP program addressing the individual, group and cultures involved in space missions. These countermeasures address areas of selection, training, pre-, in- and post-flight and monitoring as well as addressing space mission crews, ground control and mission crew families. These countermeasures need to be addressed further:

- Maintaining the presence of behavior and performance specialists through all phases of space mission design,
- Selecting full mission crews and critical ground personnel as a team,
- Embedding tests of cognitive, emotional and behavioral performance in functioning mission hardware and experiments,
- Greater use of simulators for training on board the mission,
- Further development of self report tools (personal logs, computer files),
- Developing virtual environments and telepresence to address behavior and performance aspects of missions,
- Using ground based analogs and simulators for selection and training
- Further training of mission and ground crews together.

Implications for the Medical Policy Board and Medical Policies and Requirements Document

During the year-long deliberations of the Task Force on Countermeasures, the NASA Medical Policies Board has been functioning in parallel in order to formulate a document describing the medical policies, requirements and procedures, and supplemental or interim medical selection and retention standards for the astronaut corps. The Task Force Committee applauds NASA for undertaking this important endeavor and believes that it is taking the appropriate steps in establishing fundamental policies that impact on the homeostasis of the astronaut corps. The Task Force Committee, through its series of recommendations as described in the above sections, has provided some insight and direction that should impact these evolving policies and procedures. For example, two of the primary goals of NASA are to 1) maintain the functional integrity of astronauts in order to perform unaided egress; and 2) to utilize exercise as a strategy to ameliorate deficits in cardiovascular function, aerobic exercise capacity, muscle atrophy, neurosensory dysfunction; and bone atrophy.

In meeting these objectives, NASA, first of all, must better define a standard of “fitness” among the astronauts that is realistic to an acceptable level of performance in the context of unaided egress. Also, NASA is too general in its description of the types of exercise it is using to ameliorate functional deficits in the various systems. Thus, NASA must devise an exercise prescription, incorporating aerobic, high resistance, high impact, and motor specific activities that it will use to counteract specific deficits. Further, NASA must reassess its nutritional standards and look to new strategies to insure that the astronauts are provided the best nutrition possible as the mission duration increases. Finally, in the likelihood that the Countermeasure strategies will be insufficient to meet the program objectives, NASA must invest resources to and a plan to evolve human powered centrifuge devices that may turn out to be the only effective way to maintain a fitness standard commensurate with performing unaided emergency egress after long duration exposure to microgravity.

Implementation of the Countermeasure Task Force Report

To ensure that the findings and recommendations of this report are implemented to their full potential, the CTF also recommends that NASA organize both the infrastructure and an implementation plan to achieve a set of milestones in further advancing the countermeasure program. This plan should include the following:

- 1) NASA should develop an organizational plan to perform the necessary research activities essential to improving countermeasures within the critical disciplines outlined in the report. These need to be carefully organized so that appropriate integrated ground-based research can be effectively performed.
- 2) Once appropriate milestones are achieved from the ground-based program, operations for space flight can be appropriately tested under conditions pertinent to the nature of the mission.
- 3) NASA should establish a central coordinating team to implement the countermeasure program. The team should function with the operating premise of integrating the program in such a way that components within the program do not oppose one another in achieving broad based objective across disciplines.

- 4) NASA should organize an external scientific working group to interface with the internal implementation team to provide guidance and recommendations to ensure that the countermeasure program is meeting its scientific and operational objectives.
- 5) NASA should provide yearly briefings to its appropriate advisory committees concerning the ongoing status of the countermeasure program.

APPENDICES

APPENDIX A

TASK FORCE ON COUNTERMEASURES

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APPENDIX B

SKELETAL MUSCLE DISCIPLINE - SUPPORTING MATERIAL

B-1 - Microgravity: Muscle Structure, Function, and Motor Performance

I. Introduction

This appendix presents information concerning the effects of microgravity and/or states of muscle unloading on a) the intrinsic structural and functional properties of skeletal muscle; b) the performance of muscular activities associated with locomotion and other motor tasks both during and following exposure to space flight; and c) the status of countermeasures routinely used to either maintain or prevent observed deficits in musculoskeletal function. Data from both human and animal models from in-flight and ground-based experiments are used.

A. Principles Of Muscle Homeostasis

The skeletal muscle system of adult mammalian species, including humans, is quite stable in a 1G environment in terms of maintaining normal morphological and functional properties. Although muscle protein pools undergo continuous synthesis and degradation, the kinetic properties of these pathways are such that muscle mass and protein phenotype are very stable thereby insuring the maintenance of the key properties of strength, endurance, and locomotor/movement capacity. However, in the absence of a 1G stimulus, these homeostatic properties are altered such that the ratio of protein synthesis to degradation is reduced, and the ability to maintain of protein pools and phenotypes are compromised thereby reducing the capacity of the muscle system to function at 1G. Thus, the central objective of any countermeasure strategy during spaceflight is to maintain or closely preserve the neuromuscular properties that exists at 1G.

B. Principles Of Motor Control

Under normal environmental conditions, the ability of the central nervous system (CNS) to precisely control a wide assortment of movement patterns is remarkable given the variety of conditions under which this control must be managed. All physiological systems that play important roles in the control of movement seem to be affected in one or more ways by the space environment. The supraspinal and spinal pathways of the CNS must provide for both accurate and rapid coordination of a number of neuro-sensory and motor activities regardless of the environmental conditions, i.e., 1-G versus 0-G. In considering any countermeasure to minimize deadaptation to 1 G during spaceflight it is important to recognize that spaceflight results in: 1) changes in visual, vestibular, and proprioceptive function during movement; 2) changes in coordination of activity of flexor and extensor musculature of the arms and legs in the control of body orientation and locomotion. For example, in microgravity, the relative loading of both the upper and lower extremities are markedly reduced thereby affecting both the velocity and extent of movement in performing both flexion and extension of the various joints. Further, the control of movement is shifted toward the upper extremities, hands, and fingers while relying on the lower extremities chiefly for adjusting the center of gravity.

3) Changes in the neural control of the level of motoneuron recruitment and the force generated by a given muscle or muscle group. This adjustment must be accomplished by modulating the number of motor units from each motor pool needed for a specific task in accordance with the size principle, i.e., smaller motor units recruited first and larger motor units recruited last and by frequencing modulation.

Associated with the changes in the motor activity during spaceflight, as noted above, is the occurrence of a range of detrimental effects on the functional and morphological properties of muscle. Changes in the metabolic and mechanical properties of the musculature can be attributed largely to the loss of and the

alteration in the relative proportion of the proteins in skeletal muscle, particularly in the muscles that have an antigravity function at 1G. These adaptations could result in decrements in the performance of routine or specialized motor tasks both of which may be critical for survival in an altered gravitational field, i.e., during spaceflight and during the return to 1G. For example, the loss in extensor muscle mass will require a higher percentage of recruitment of the motor pools for any specific motor task. Thus, a faster rate of fatigue will occur in the activated muscles. Thus, it would appear to be an advantage to minimize muscle loss during spaceflight, at least in preparation for the return to 1G after spaceflight. New insights into the complexity and the interactive elements that contribute to the neuromuscular adaptations to space have been gained from studies of the role of exercise and/or growth factors as countermeasures of atrophy. The present section of the report illustrates the inevitable interactive effects of neural and muscular systems in adapting to space. Only modest progress has been made toward understanding the physiological and biochemical stimuli that induce the neuromuscular adaptations to space.

II. Effects Of Microgravity And Simulation Models On Skeletal Muscle Function

A. Observations on Animals (Rodents):

This section summarizes research concerning the effects of altered loading states on the morphological, functional, and molecular properties of mammalian skeletal muscle. The discussion examines both ground based models (i.e., hindlimb suspension) and spaceflight missions (Cosmos Missions and Space Life Sciences 1 and 2) involving adult rodents whereby the amount of weight bearing chronically imposed on the muscle(s) is markedly decreased thereby inducing a change in the amount and type of protein that is expressed in the targeted muscles. In each of these settings, a number of adaptations occur. These include:

- 1) Atrophy of both slow-twitch and fast-twitch fibers comprising ankle and knee extensor muscles used for both weight bearing and locomotion.
- 2) A change in contractile protein isoform expression in a select population of fibers reflecting a faster phenotype for controlling both cross bridge and calcium cycling processes, i.e., the primary pathways for energy consumption in performing mechanical activity.
- 3) Corresponding changes in the functional properties of the muscle manifesting a speeding of shortening and relaxation properties.
- 4) A reduction in both the absolute and relative force and power generating properties of antigravity and locomotor muscles.
- 5) A shift in the force frequency patterns of antigravity muscles whereby a greater frequency of electrical stimulation (i.e., action potential frequency) is needed to generate submaximal levels of force output.
- 6) A shift in the intrinsic substrate utilization profile of the muscle whereby the capacity to oxidize long chain fatty acids is reduced relative to that of carbohydrate.
- 7) An increase in enzyme levels supporting the pathways of glycogenolysis and glycolysis.
- 8) Corresponding increases in the fatigability of muscle groups most likely due to both a reduction in the balance for energy supply to energy demand within a given motor unit and a demand for the expanded recruitment of faster motor units with less resistance to fatigue.

9) A reduction in the oxidative properties of large dorsal root ganglia cells and in small motoneurons, which could impact the function of both sensory and motoneurons.

B. Observations on Humans

Based on over 40 years of experiments from the Russian space program as well as the U.S. space program, including the Apollo and numerous space shuttle flights, a number of observations have been made which demonstrate a wide range of effects on the motor performance of humans. Some of these effects are:

- 1) Loss of skeletal muscle mass, particularly in those muscles groups that function at 1G to maintain extension against normal gravitational loads, often referred to as antigravity muscles.
- 2) Reduction in the ability to exert maximum torque at varying velocities of movement, but particularly at the lower velocities of movement.
- 3) Reduction in size of slow and fast muscle fibers
- 4) Increase in the proportion of fast myosin in some fibers within two weeks of exposure to spaceflight.
- 5) Diminished ability to maintain a stable standing posture.
- 6) An imbalance of the relative bias of activation of flexor and extensor muscle groups, with greater bias toward flexion at 0G.
- 7) Reduced threshold of the stretch reflex combined with reduce sensitivity to stretch, i.e. less gain in responsiveness at a given level of stretch.
- 8) Modified sensitivity to cutaneous vibrations to the sole of the foot.
- 9) Increased susceptibility to fatigue during a given motor task upon return from 0G to 1G.
- 10) Altered perception of postural position at 0G and upon return to 1G.

III. Functional Significance of Adaptations to Spaceflight

A. Effects On The Control Of Movement

Perhaps the condition in spaceflight in which control of movement is most critical for crew safety is during extravehicular activity (EVA). There are several reasons for the danger associated with EVA. Other than the dangers of solar flares and the remote chance of collision with meteorites, the engineering of the EVA suit, the procedures for pressurizing the suit and the specialized tools needed in EVA can have a high impact on the success of space missions. The space suit, of course, must be pressurized to a

level sufficient to avoid the "bends". This situation presents a very significant challenge to engineers primarily because of the required mobility of the arms and head. For the legs, joint mobility is less important but this control is still a factor in the maneuvering of one's center of gravity. The mobility problem with the upper limbs is that the space suit pressure provides resistance to movement of the shoulders, elbows and fingers. Overexertion of the arms can easily become a limitation in work performance in EVA. Even well before the onset of neuromuscular exhaustion, a reduction in the quality of performance is almost certain to occur. Perhaps, the greatest fear in EVA should be the loss of concentration and attention associated with the greater susceptibility to discomfort and pain which accompanies localized muscle fatigue. A single critically inaccurate movement resulting from these types of distractions could cause an accident. Human factors such as these will impact safety as well as productivity if accommodations in the design of space crafts and related facilities such as a space station are not made. At one stage in the planning of this station, it was being assumed by the architects that there would be as many as 6-8 hours of work per day during EVA and that this would be repeated several days per week while constructing the space station "Freedom". Fortunately, this is no longer the case. The critical question remains, however, "What is an acceptable work schedule given the EVA apparatus to be used?".

The glove of the pressurized space suit presents one of the greatest limitations to work productivity in space. The fine control of the fingers is reduced markedly. There is the obvious loss of the usual touch sensations. In addition, the fingers must grasp objects by overcoming the restrictions in the basic design of the glove and the elevated atmospheric pressure within the glove which creates considerable resistance to grasping movements. The tips of the fingers have become chaffed from the continuous abrasion between the skin and the internal surface of the glove during prolonged EVA tasks. One way to minimize some of these limitations in hand control and other associated limitations in the absence of gravity, has been to devise special tools for EVA activities. During the development of specialized tools for EVA, their use often requires extensive practice in underwater simulations. An additional challenge in the design and use of tools specialized for EVA tasks is the limitation in visibility inherent in the helmet of the spacesuit. The curvature or wrap-around visor of the helmet causes some visual distortion. This distortion actually may be more of a problem in the practice sessions underwater than in space because of the greater refraction due to water. On the other hand, the diffraction caused by the water results in an enlarged image, an advantage that is not available during repair tasks in space.

In planning the construction of structures in space, considerations of human factors must be at a level of sophistication which transcends the point of view that an astronaut or cosmonaut can perform some physical task and survive. Safety and the optimization of productivity in human performance need more emphasis in efforts to expand human presence in space.

When humans enter a microgravity environment, there is an immediate and dramatic reduction in the activation of the extensor musculature required to maintain an upright posture at 1G. The electrical activity (electromyography, EMG) of flexor and extensor muscles in the resting position of the neck, trunk, hip, knee and ankle reflect a generalized flexor bias in flight compared to 1G. This bias has been observed during spaceflight in astronauts when asked to stand upright and this effect is independent of whether or not their feet are anchored to a surface. Further, when they are asked to stand erect with a few degrees of forward tilt, the magnitude of the forward tilt may be as much as four times greater (~12 vs 3°) at 0G than 1G, indicating a relative decrease in extensor activity and/or increase in relative flexor activity. The sites and kinds of sensory information that trigger this exaggerated forward tilt are not understood. This residual flexor bias even after returning to 1G provides a clear indicator of a general adaptation strategy for organizing movements in a 0G environment.

Although a flexor bias persists during flights even after adaptation to 0G, the activity levels of some of the extensor muscles progressively increase within a few days of continued exposure to the 0G environment. This recovery of extensor activity and continued elevation of flexor activity has been clearly documented in ground-based models of weightlessness. For example, extensor EMG activity essentially disappears immediately upon unloading of the hindlimbs in rats. Within hours, however, some EMG activity reappears during continued hindlimb suspension and by 7 days the total daily amount of activation is near normal levels. This pattern has been observed in both predominantly slow (e.g., the soleus) and fast (e.g., the medial gastrocnemus) ankle extensors. In contrast, the EMG activity of the tibialis anterior, an ankle flexor is significantly elevated throughout the suspension period. The "recovery" to normal or near normal levels of extensor EMG activity while remaining "unloaded" suggests that the CNS is "programmed" so that general extensor bias continues as it does at 1G under normal gravitational loads. This apparent residual bias may have been permanently acquired during development as a result of the daily sensory cues of a 1G environment. Alternatively this extensor bias could be inherent in the design of the CNS, i.e., independent of any activity-dependent events associated with movement control in a 1G environment.

The ability to perform movements, including posture and locomotion at 1G, is adversely affected by exposure to as little as one week of spaceflight. All crew members tested to date have experienced some postural instability for 1-2 weeks, or even longer in some instances, following spaceflight. This instability, which varies markedly from crew member to crew member, reflects alterations in perception, sensitivity, and responsiveness. In many cases the altered motor functions may not be readily apparent due to use of compensatory mechanisms such as maintaining a wider stance, taking shorter steps, greater dependence on visual cues and generally being more cautious.

There are a number of physiological measures which reflect altered movement control following spaceflight, particularly altered postural responses to horizontal perturbations e.g. unusual magnitudes and durations of activation of extensor and flexor motor pools. Based on studies of the visiting crews in the Salyut-6 missions ranging in duration from 4-14 days (most for 7 days), the EMG response of the soleus and tibialis anterior to perturbations of the standing position was almost doubled and the response time to the perturbation was 3 times longer after than before flight. Severe postural disruptions following 4-10 days of spaceflight on the shuttle also have been reported. A rapid recovery rate was evident immediately after flight with most of the recovery occurring within the first 10-12 hours post-flight followed by a slower recovery over the next 2-4 days. Further, it was estimated that 50% of the recovery occurred within 3 hours postflight. Adverse postural effects, however, persisted for as long as 42 days after a 175-day flight.

As was true for performance in a maximum torque-velocity test of the plantarflexors, the duration of the spaceflight has proven to not be an important determinant in the severity of postural stability. For example, cosmonauts that had been on the Mir station for 326 days had a similar EMG amplitude response to postural perturbations immediately after flight as before flight. In contrast, the EMG response was doubled in cosmonauts from either a 160-day or a 175-day spaceflight.

Another clear example of the modification in the input-output ratio of the motor system was demonstrated after 7 days of dry immersion. Before immersion the subjects were able to increase the force in relatively constant increments up to about 50% of maximal voluntary contraction in a succession of about 10 trials. After flight, the subjects overestimated the target force considerably even at the lower force levels and the force differential became even more distorted at the higher torques.

Although many adaptations are clearly manifested during the performance of motor tasks at 1G, after having adapted to spaceflight conditions for a specific duration, many details regarding the specific adaptations to spaceflight are not available because of the absence of well-controlled experiments. All studies of humans reflect some unknown combination of the effects of the spaceflight conditions, the measures used to counter spaceflight effects, and the individual differences in responsiveness to both spaceflight and the countermeasures used.

Body movement perception is affected when the magnitude of the gravitational vector is altered. There are immediate and longer-term effects of these altered forces on perception. It is clear, for example, that there are disturbances in oculomotor control, vestibular function, pain sensitivity, muscle stretch sensitivity, joint position sense, and cutaneous sensitivity to vibration, all of which may play some role in modification of motion-position perception in response to spaceflight. Altered perceptions of speed of movement, the effort it takes to perform a movement, and movement of the body relative to its surroundings have been reported when alternating periods of 0G and 2G are imposed during parabolic flights. When subjects raised or lowered their body from a squat position during the 2G phase of the parabolic flight, perceptual distortions of movement were evident. These findings were interpreted as indicating that the motor control of skeletal muscles had been calibrated to a 1G reference level, and that these illusions resulted from mismatches between the efferent control signals and the expected patterns of associated spindle activity.

These studies were continued using perception of upper limb position during parabolic flights, with and without vibration of the biceps or triceps brachii tendons. Because tendon vibration is thought to activate sensory Ia and to some extent IIa afferent fibers from the muscle spindles, and because these receptors are thought to be sensors of angular displacement, these studies provided some insight into the potential role of spindles in the diminished accuracy of position sense observed after spaceflight. The perceived magnitude of displacement from the apparent limb position upon tendon vibration was $1.8G > 1G > 0G$. The subject's perceptions of displacement were consistent with the actual displacements. The results of these experiments suggest that higher G forces on the body required greater postural tonus and an altered gain for the muscle spindles.

Many astronauts have reported that they are not aware of the position of their limbs when they shut their eyes to sleep or relax while weightless; one crew member stated, "It is almost as if the limbs are gone". When they tense their muscles, the position sense returns. One explanation for this phenomenon is not that sensitivity of the receptors is blunted, but that the stimulus is reduced. Interestingly, this sensation is the antithesis of the phantom-limb phenomenon described by amputees, i.e., sensing the presence and even the movement of a limb even though the limb has been amputated. A consistent observation by those who have experienced 0G for prolonged periods has been upon return to 1G a sensation of heaviness of the body, particularly of the head. Although the selective atrophy of the extensor musculature associated with weightlessness could contribute to this sensation of heaviness. This is not the only factor given that this sensation of heaviness disappears rapidly within a few hours in some crew members. Performing a task with atrophied muscles will require a sense of greater effort than normal since more motor units must be recruited at a higher frequency of activation. In turn, this elevated recruitment is likely to increase the activation of muscle proprioceptors.

The ability to produce maximum plantarflexor torque at velocities ranging from 0 to 180 °/sec is reduced in short-term (7-14 days) and long-term (75-237 days) spaceflight. After short-term spaceflight maximum isometric torque decreased by 18% and at 60 °/sec by 38%. After long-term spaceflight

maximal torques were 25, 12, 10 and 18% lower than preflight values at 0, 60, 120 and 180 °/sec, respectively. The changes in torque among the cosmonauts varied considerably ranging from -60 to +15% of preflight values. Although muscle atrophy almost certainly contributes to the reduced torques commonly observed after short- and long-term spaceflights, the characteristics of neural activation of the motor pools also are affected. The highly variable losses in torque at high speeds in some cases and at low speeds at others cannot be easily explained by changes in the muscle properties alone.

Some of the adaptations in the motor responses noted above may reflect, at least in part, the effects of muscle atrophy. The reduced force potential could exacerbate the postural instability of the astronauts and cosmonauts usually attributed to the neural control system upon return to 1G. This possibility seems particularly feasible since the fibers innervated by the motoneurons that have the larger role in maintaining routine posture (i.e., the slow motor units) are the ones that seem to atrophy the most. Further, if the nervous system is not aware of the reduced muscle force potential and does not adjust the output signal accordingly, then the motor output will be reduced. This inappropriate neural input to output relationship will result in an exaggerated movement or sway during standing and may even result in the loss of balance.

In summary, during and after spaceflight the effectiveness of the neuromotor system clearly is compromised. There could be a degradation in functioning of the muscles, synapses within the spinal cord, reception of sensory information by the brain and, in some cases, interpretation and perception of the environment. Dysfunction at any one of these levels at some critical time during a flight could have a major impact on the success of a mission and the safety of the crew members.

B. Implications of Neuromuscular Adaptations for Rapid Egress Capability

The possibility for the need for a rapid egress in case of an accident upon reentry has been reconsidered since the Challenger accident. While some improvements have been made in preparing for an accident upon landing of the shuttle, a clearer understanding of the performance capability of crew members in such a scenario is needed. For example, how rapidly will the crew members be able to escape from the craft in case of an emergency? Based on the experience of both the cosmonauts and the astronauts, it is apparent that the ability to egress suddenly will be limited unless effective countermeasures for the loss of neuromuscular performance are identified and adhered to rigidly during prolonged spaceflights. However, another limiting factor in the egress potential is the flight gear that are worn in reentry. This gear provides significantly elevated loads and heat challenges that could limit egress regardless of success of any countermeasure.

IV. Mechanisms of Striated Muscle Plasticity In Response To Weightlessness

This section examines the effects of unloading on the potential stimuli likely inducing the muscle adaptations to spaceflight as well as the cellular/subcellular processes involved in the adaptive response. Adaptations occurring at the cellular level that result in a change in the quantity and/or quality of protein expression in response to reduced mechanical activity can be regulated theoretically at several levels of control involving transcriptional, pretranslational, translational, and post translational processes. In considering the types of adaptations reported above in the rodent model, available evidence suggests that all of these processes are likely playing a pivotal role.

A. Neuromuscular Activity And Its Role In Plasticity

1. Hindlimb Suspension

Adaptation to chronic unloading of skeletal muscles is determined in part by the manner in which the muscles are activated. The activity patterns of the soleus, medial gastrocnemius and tibialis anterior muscles have been monitored from the same chronically implanted intramuscular electrodes before and during one-month of hindlimb suspension. Total daily EMG activity (mV.sec), measured in the soleus and medial gastrocnemius, was significantly reduced on the day of suspension, was similar to control levels by 7-10 days post-suspension and continued at near-normal levels for the remainder of the experimental period. Daily EMG levels of the tibialis anterior were above normal during all post-suspension days. In addition, the interrelationships of the EMG amplitude patterns, a reflection of the recruitment patterns, between the soleus and medial gastrocnemius were altered on the day of suspension, but recovered to a normal pattern by day 7 post-suspension. These data indicate that the neural mechanisms controlling hindlimb muscles initially change in response to the unloaded environment, but might return to normal within a short period of time after the suspension began.

Riley et al. digitized 16 min of continuous EMG activity per day from the soleus on presuspension days 7 and 4, as well as after 4 and 7 days of suspension. Average total time of soleus activity (normalized per hour) in suspended rats was about 12% when compared to presuspension values and the activity was reported to have a "phasic" compared to a "tonic" pattern. The amplitude (root mean square) of the signals was smaller (25-50%) during compared to before suspension. Bonen et al. recorded 90 minutes of activity from the soleus and plantaris muscles (both primary ankle extensors) over several days before and after suspension; both overall mean amplitude and frequency of motor unit action potentials (based on a "turns analysis") were significantly decreased during suspension compared to normal cage activity.

These data indicate a general decrease in activation duration and amplitude of extensor muscles during the first week of suspension. On the other hand, after longer periods of unloading extensor EMG activity may return to normal. Although chronic tension levels in muscles of suspended rats have not been recorded, it is reasonable to assume that forces in the plantarflexors were small. In addition, it is likely that the plantarflexors were further unloaded when in the plantarflexed position, the usual position during suspension. In contrast, loads on the tibialis anterior were most likely slightly elevated with the muscle maintained in a "stretched" position. It seems unlikely, however, that the greater activity (3-4 times) of the tibialis anterior was due to increased stretching of the muscle during suspension compared to that during routine cage activity since most muscle stretch receptors accommodate rapidly to sustained stretch. In any case the effects of suspension on the actual loading properties of muscle need to be substantiated by recording muscle forces pre-, during, and post-suspension.

2. Spaceflight

The effects of spaceflight on the chronic neuromuscular activity in rats are less substantiated than for hindlimb suspension. Presumably muscle forces during spaceflight would be minimal, although no force data are available. In humans during spaceflight the tonic activity (EMG) of the soleus (a plantarflexor) is reduced, whereas the tonic activity of the tibialis anterior (a dorsiflexor) is enhanced during postural adjustments. This activity reversal of extensors and flexors normally observed at 1G has also been reported during parabolic flights in humans and in monkeys after short-term flights. No chronic EMG or muscular force data from either humans or animals during spaceflight have been published.

B. Reductions in Muscle Strength and Power

Studies on both humans and animals clearly show that the force generating capacity of extensor muscles of the hindlimb are reduced to varying degree following either spaceflight or hindlimb unloading. This reduction has been attributed to a) a decrease in muscle mass reflecting a reduction in the cross sectional area of the muscle fibers; b) a reduction in the capacity to activate the muscle via supraspinal pathways; and c) a reduction in the specific force of the muscle (reduced force corrected for fiber cross sectional area). While it is reasonable to conclude that the reduced force due to atrophy is due to a loss in contractile protein contributing to the contraction process, the underlying mechanisms responsible for the inability to activate the motor unit pool is poorly understood. The same holds true for the factors involved in the reduction in specific tension. Clearly more extensive research is needed on this important problem.

C. Mechanisms of Muscle Atrophy

During states of hindlimb unloading the rate of total protein synthesis (a translational process) is significantly reduced within the first few hours of creating the unloaded state. This is coupled to a subsequent transient increase (over the next several days) in the net rate of protein degradation thereby resulting in a ~ 50% smaller protein pool comprising the muscle, i.e., the muscle becomes significantly atrophied. While both the initiating events and the signal transducing process(es) associated with the atrophy response remains largely unknown (see above), the involvement of either growth factor(s) down regulation or the catabolic actions of other hormones appear to be involved. For example, mRNA signals for insulin like growth factor-1 (IGF-1) expression in skeletal muscle is reduced in hindlimb muscle when the weight bearing activity of the animal is reduced. In contrast, recent findings suggest an opposite response when a skeletal muscle is functionally overloaded, i.e., IGF-1 expression is enhanced. Recent studies on cardiac muscle further suggest that IGF-1 expression is linked to the loading state imposed on the system. Whether there are additional hormonal factors involved in the atrophy response is uncertain.

In this context, there appears to be a critical interplay between mechanical factors and growth-stimulation factors such as growth hormone in the maintenance of muscle mass when challenged by a state of unloading. Furthermore, it has been shown that the time course of the muscle atrophy response to unweighting is altered when cellular glucocorticoid receptors are pharmacologically blocked. Also, under conditions involving muscle wasting in response to exogenous glucocorticoid treatment, a key enzyme, glutamine synthase, is upregulated by elevations in the circulating level of this hormone. This enzyme is thought to regulate both the formation and release of the amino acid, glutamine (i.e., the primary amino acid to which most amino acids are converted during the protein degradation process) from the muscle during the wasting process. Experiments in which the level of glutamine is artificially elevated in both the plasma and muscle during glucocorticoid treatment, markedly reduces both the atrophy process and the decrease in total protein and myosin protein synthesis rates that occur under these conditions. On the other hand, agents that are thought to inhibit the proteasome axis component in the cascade of protein degradation processes appear to be partially effective in ameliorating the atrophy response to weightlessness. The above information clearly illustrates that more basic research is needed to examine the interaction of hormonal and activity factors in the regulation of protein synthetic and degradation processes, especially in the context of the atrophy response associated with muscle unloading.

D. Alterations In Myosin Phenotype

Recent findings involving both cardiac and skeletal muscle suggest that transcriptional and pretranslational control of the slow MHC gene is highly regulated by thyroid hormone (T3). For example, T3, in conjunction with its nuclear receptor and other nuclear regulatory proteins, acts as a negative modulator of transcription of the beta (slow or type I) MHC gene while concomitantly exerting positive transcriptional control of the cardiac fast, alpha MHC gene. Thus, it is interesting that the down regulation of the slow myosin gene typically seen during states of unloading can be inhibited by making the animals hypothyroid. Collectively, these findings suggest that changes in loading state may alter the muscle's responsiveness or sensitivity to thyroid hormone. Furthermore, recent findings on cardiac muscle also suggest that transcription of the beta (slow, type I) MHC gene can be positively regulated by expression of a nuclear factor(s) that binds to a specific DNA sequence (designated as beta e2) upstream of the gene's transcriptional initiation site. This factor can be upregulated in the rodent heart in response to pressure overload. Thus, there appears to be a complex interaction of mechanical (loading state)- and hormonal-induced transcriptional factors that are involved in regulating MHC plasticity in response to altered states of muscle loading. Understanding the regulatory factors associated with slow-myosin gene expression is important, because it is predominantly the slow-myosin isoform that is sensitive to gravity state. Further, motor units expressing slow-myosin are the one's predominantly recruited for posture control and low intensity movements.

V. Fundamental Concepts Impacting the Effect Of Countermeasures

A. Basic Physiological Principles For Developing Exercise Countermeasures

Any exercise-related countermeasure for the preservation of skeletal muscle function will be manifested via the spinal mechanisms which regulate the order and number of motor units recruited. In essence, all movements represent the net effect of the number of motor units recruited and which combination of motor units for each muscle that will be recruited, combined with the mechanical restraints placed on the muscles. The selection of which and how many motor units will be recruited is defined in some manner when kinematic features of the motor task is selected. Muscle activity also can be imposed by electrical stimulation of its nerve where it is generally assumed that the most readily stimulated muscle fibers will be those innervated by the largest axons (and thus probably belonging to the largest motor units). Such a recruitment order determined largely by axon diameter, is opposite to that normally used by the central nervous system. Otherwise, the same general principles as addressed below apply to electrical stimulation of muscle as a potential countermeasure.

In designing an exercise countermeasure, the major variables to modulate are the "level of effort", i.e., the number (and frequency to some degree) of motor units recruited, and the speed at which the muscle will shorten or lengthen. For any given level of recruitment, the changes of muscle length will be defined by the mechanical conditions under which the motor units are activated. The force produced will be a function primarily of the number of motor units (and thus muscle fibers) recruited, and the mechanics which define the velocity and direction of movement. Because the force-velocity relationships are somewhat predictable, the "types" of exercise (high resistance, high power, low resistance, etc.) largely reflect of the number of motor units recruited and the temporal pattern for their recruitment. Whether that force is sufficient to shorten or lengthen the muscle and at what speed the displacement will occur depend on the loading conditions. A high resistance exercise is one in which a high proportion of the units within the appropriate motor pools are recruited and a high load is imposed,

resulting in a relatively slow velocity of shortening. If the same recruitment pattern occurs and the load is reduced, then the velocity of movement will increase hyperbolically.

Although these basic physiological concepts derived from isolated (e.g., in situ) experiments are well recognized and generally accepted, they have not been translated into a rational and systematic approach for developing more effective countermeasures for the neuromotor deficits that develop during prolonged spaceflight. Further, a more integrative rather than reductive approach to motor performance is needed. A more integrative physiological perspective also must be maintained in assessing exercise countermeasures with respect to the metabolic consequences and the corresponding adaptations to spaceflight and exercise. Given the interdependence of the motoneuronal and muscle metabolic properties, however, recruitment and metabolic responses of recruitment are essentially inseparable.

Relevant questions for maintaining normal muscle tissue properties appear to be the following: 1) What combinations of forces and velocities will most efficaciously maintain the normal physiological status for each type of motor unit and muscle fiber type? 2) What are the differences in the responsiveness of fiber types and muscle types to specific muscle force-velocity events? For example, does this responsiveness differ in arm versus leg, flexor versus extensor, etc. musculature? and 3) What durations and intermittencies, i.e., work-rest ratios of the mechanical stimuli are necessary to maintain a muscle fiber?

An implied assumption in the above questions is that there are some mechanical event(s) associated with exercise that produce the necessary stimuli for cell maintenance. However, these stimuli could be metabolic or some other event related to excitation-contraction coupling. In any case, the same considerations of the variables noted above would be appropriate for each potential physiological modulator.

B. The Quantity of Activity Needed for Muscle Homeostasis

To counter the atrophic effects of spaceflight one needs to know the means by which the space environment induces the flight effects. Two of the prevalent hypotheses are that muscles atrophy during flight because of a reduction in 1) the activation of the muscles; or 2) the muscle forces associated with the reduction in activation. For example, a common concept which has prevailed for many years is that muscles enlarge when they are active and atrophy when they are inactive. Further, a linear and direct relationship between muscle fiber size and neuromuscular activity or exercise level is often assumed. It is clear, however, that this assumption is incorrect or at least misleading. For example, within a given muscle those muscle fibers which are used (i.e., recruited) the least often are usually the largest fibers. Analyses of biopsies from endurance-trained swimmers and weight-lifters also illustrate that the amount of activity is poorly correlated with fiber size. Thus, it is apparent that the effectiveness of an exercise as a countermeasure for muscle atrophy cannot be based solely on the quantity (total time, number of repetitions, etc.) of exercise. To maintain muscle mass, it appears that a relatively small amount or duration of activity per day is needed and that the amount needed varies widely among fiber types and specific muscles. The more important factor appears to be the mechanical load on the muscle during activation. This view certainly appears to be true in hindlimb suspended rats when the animals are exercised intermittently. These studies suggest that 6 minutes per day of climbing a grid with attached weights (i.e., a relatively high load exercise) had a similar effect of ameliorating muscle atrophy as 90 minutes of daily treadmill exercise (i.e., a relatively low load exercise). Whether a rat exercises for a few minutes or up to 2 hours per day, similar effects are observed on the muscle mass in hindlimb suspended

rats. Thus, some minimum amount of muscle activation and force may be required to maintain muscle mass.

In defining exercise protocols and devices to counter the effects of spaceflight on skeletal muscle, the most efficacious exercise may be unique for each muscle group, e.g., extensors vs flexors and muscle type (i.e., muscles that are comprised predominantly of slow vs fast fibers). Further, an exercise regimen that may prevent muscle atrophy may not be the most efficacious in preventing demineralization of bone. It seems likely that reasonable compromises in exercise prescriptions during spaceflight can and must be defined so that a crew member will not need to exercise several hours each day in order to maintain an acceptable functional state while spending prolonged periods in space and during periods of reduced gravitational forces while on the moon or Mars.

C. The Impact of Activity-Hormonal Interactions

Neuromuscular activity may play a facilitatory rather than a direct role in maintaining muscle mass. For example, it is becoming increasingly obvious that there can be important interactive effects between exercise and hormones. Glucocorticoids can induce marked and selective atrophy of fast muscles, and weight-lifting or treadmill exercise during glucocorticoid administration can greatly reduce the severity of the atrophic response. Similarly, growth hormone alone can significantly decrease the severity of atrophy induced by hindlimb suspension of rats. Interestingly, this effect is greatly amplified when the growth hormone treated suspended rats are exercised (climbing a 1 meter grid inclined at 85° with weights attached as little as 15 times/day). Further important examples of activity and growth factors are discussed above in, "Mechanisms of Muscle Atrophy".

D. Defining the Acceptable Limits of Muscle Dysfunction in Microgravity

From an operational point of view, some consensus needs to be formulated regarding how much loss of function can be tolerated without a significant compromise in safety and possible long term consequences. For example, one 10-min exercise period per day may be sufficient to maintain 90% of normal function of the extensors of the ankle, knee, hip, trunk and neck, while it may require 90 min/day to maintain 95% normal function. Does 90% of normal function provide an acceptable margin of safety? Similar operational issues are relevant for each physiological system. Also individual differences among the flight candidates should be taken into account, in particular since the results from virtually every study of spaceflight and ground-based models of spaceflight have demonstrated marked individual differences in the response of the neuromuscular system. These unique individual responses may hold the key to a better understanding of the etiology and magnitude of these specific effects. An integrative physiological perspective and experimental approach in determining the adaptability of humans to spaceflight is essential.

E. Lessons Learned From Ground Based Models on Humans

In humans, one model which has been used to study the effects of changing gravitational loads on the neuromuscular system involves wearing a weighted (~13% of body weight) body vest throughout the waking hours. Bosco and coworkers have shown that wearing this weighted vest for 3 weeks resulted in a shift to the right in the force-velocity curve and an increase in the power generated during squat

jumping in highly trained athletes. The authors suggested that the subjects had acclimated to a 1.1G environment and when the load was removed for the final testing, the subjects were experiencing the relative sensation of a 0.9G environment. Because of the relatively short experimental period (i.e., 3 weeks), the adaptive responses were thought to be more related to neurogenic (e.g., greater effective activation of motor units) than myogenic (e.g., fiber type adaptations or hypertrophy) factors. It is clear, however, that muscle atrophy occurs very rapidly in response to flight. For example, the rat soleus can atrophy by 25% within 4 days of the initiation of flight. Furthermore, it appears that significant atrophy can occur in humans after 5-11 days of flight.

Kuznetsov and co-workers studied the effects of bedrest with head-down tilt for 30, 120 and 360 days on the size of gastrocnemius fibers. Thirty days of bedrest resulted in ~15% atrophy in both slow and fast fibers. Treadmill exercise of a moderate intensity for 60 min/day for the first 24 days and 120 min/day for the last 6 days did not ameliorate the atrophy. In fact, the fast fibers in the exercised group were 27% smaller than control compared to the non-exercised group. The longer duration study involved two exercised groups. One group started exercising early in the experiment (at 21 days) and included relatively strenuous passive, strength building and locomotor exercise. The second group started a relatively milder exercise program on day 121. The duration of the exercise was either 60 or 120 minutes. Early onset of exercise resulted in the maintenance of fiber size nearer to control values at both 120 and 360 days. The overall mean fiber size was decreased by ~40% in the second group and only by ~15% in the first group. These data suggest that acclimatization to any exercise routine during the early phase of long-term flight, when the rate of atrophy is the highest, may have a significant residual effect by maintaining a critical level of responsiveness to exercise training during the latter phases of a mission.

Greenleaf et al. studied the effects of 30 days of bedrest at a -6° tilt in healthy men. Two groups of subjects exercised in the supine position for two 30-min periods/day 5 times per week. One group performed short-term variable intensity isotonic exercise while the other group followed an intermittent high-intensity isokinetic program. All subjects were tested weekly for muscle performance and peak oxygen uptake. Compared to control, peak torque for the knee extensors progressively decreased showing an ~12% decline after 4 weeks. The peak knee extensor torques were not significantly different among the two exercise trained and the control groups. No consistent effect of bedrest or exercise was observed for the knee flexors.

Cherephakin and co-workers studied healthy males after 7 weeks of bedrest (-4 to 6° tilt). In 3 subjects, the cross-sectional area of the "red" and "white" fibers of the soleus decreased by an average of 28 and 35%, respectively. Some lysis (separation of myofibrils) was evident in the fibers. Leg circumference was decreased by 13% and endurance time for a bicycle test was decreased by 10% following bedrest. The strength of the postural muscles was significantly decreased as well. When a combination of exercise (intermittent bouts of bicycling at a relatively high heart rate in the antiorthostatic position) and electrostimulation was used (25-30 min/day, once or twice/day), the magnitude of all of these adaptations was reduced. In a static endurance test, exercise before electrostimulation had a more positive effect (52% increase) than exercise after electrostimulation (36% increase). During a 30 day bedrest study, 3 subjects had their knee and ankle extensors and flexors in the dominant leg stimulated twice daily for a total of 40 minutes per day on a 3-day on and 1-day off schedule. The electrical stimulation program appeared to have a slight beneficial effect on maintaining the torque-velocity properties of the knee extensors, but not the knee flexors, during the bedrest period. As stated by the authors, however, these data were preliminary and quite variable.

The effectiveness of specific exercise protocols to counter the effects of long-term bed rest on neuromuscular performance has been studied. In a 182-day 40° head-down tilt bed rest study, 18 normal subjects were assigned to three groups: 1) those who exercised with protocols similar to those generally used by cosmonauts on the Mir station; 2) those who exercised about half that intensity; and 3) those who did not exercise. Two measures of neuromotor performance made before and during bed rest were the maximal plantarflexor torque (60 °/sec) and the EMG amplitude associated with a fixed plantarflexor effort requiring about 10% of the maximum torque. Subjects who exercised at the highest level showed no change in either parameter throughout the study. Subjects who exercised at half that level (i.e., similar to MIR station protocols) showed no loss of maximal torque, but the torque: EMG amplitude ratio was only one third of pre-bed rest levels. For the no exercise group, maximal torque declined by about 40%, while the torque: EMG amplitude ratio declined by 59% at 182 days. These data suggest that exercise protocols similar to those used in spaceflight are sufficient to maintain neuromuscular torques for prolonged periods without weight-bearing. It also appears that reducing the exercise volume by half results in some loss of function, but the loss may be principally in the neural system.

Based on the evidence available to date from laboratory animals and humans, the mass of the extensor muscles of the legs, hip, trunk and neck are likely to be the more difficult ones to maintain. It also appears that these muscles will be affected the most by spaceflight. This might be expected because the difference in the functional demands of these muscle groups at 1G compared to 0G will be greater than for those muscle groups which have less of an antigravity function.

A key question is: "How much and what pattern of activation and resulting force is essential per day to maintain muscle mass?" For each physiological property of the muscle or each muscle protein, the same question must be asked. Further, it remains to be determined whether the altered activity and force patterns in spaceflight are the primary stimuli that account for the changes that occur in the muscles. For example, modulation of hormonal and/or other tissue growth factors during spaceflight also may contribute to the etiology of spaceflight-induced muscle atrophy.

F. Confounding Problems In Assessing the Effectiveness of Countermeasures

The effectiveness of existing exercise protocols and descriptions and recommendations of new exercise protocols based on the requirements of astronauts to perform intravehicular and extravehicular activities in microgravity is an evolving process. From the start of the human space program significant attention has been given to the question of how to counter the potential (expected) detrimental effects of spaceflight on the neuromotor system. This issue has not been resolved largely because the "pure" effects of microgravity have not been elucidated and thus it is not clear what effects must be countered. Also contributing to the delayed resolution of this issue has been the occasional absence of full and accurate disclosures of the actual physiological impact of spaceflight on some crew members. It is evident that the postflight physiological status of crew members reflects the net effect of the individualized countermeasures (exercise and others) and the adaptive effects of spaceflight itself. Despite these limitations considerable insight has been gained by carefully observing a wide range of responses to many flights of varying in duration. In one 5-year period (1982-1986), during the Salyut-7 flights and the first year of the Mir space station, 21 crew members accumulated 2,208 person days in space (7 crew members with more than 130 days and 2 with 366 days). These cosmonauts performed 97 person hours in extravehicular activity with 2 crew members accumulating almost 32 of those hours.

Based largely on observations of 24 crew members from Salyut-6 and Salyut-7 missions and on the Mir station, Kozlovskaya and co-workers suggested that the effects of microgravity on the motor system are

defined by at least 3 factors: 1) duration of exposure; 2) individual differences in sensitivity and responsiveness to flight, and 3) characteristics of the exercise regimens. The duration of the flights ranged from 60-366 days. Fourteen of the 24 cosmonauts visited the space station for the first time. For four of the crew members, the long-duration flights had been preceded by a flight of about 7 days, while 7 others had already experienced long-term spaceflights. Data were collected before flight and 2, 4, 6, 11, and 45 to 72 days after flight. Analysis of the motor responses of these 24 crew members led to reasonably clear conclusions regarding the effectiveness of exercise as a countermeasure for spaceflight-induced motor deficits. When the subjects were ranked according to their motor capacity upon return to 1G, the intensity and volume of exercise training during the spaceflight were very highly correlated with this ranking. In contrast, there was a negative correlation between the flight duration and the ranking of the motor capacity at recovery; the motor capacity was generally better in those cosmonauts who had flown for the longer periods of time. Individual differences in "space tolerance" among cosmonauts may reflect the differences in the utilization of the prescribed countermeasures because participation and the details of the countermeasures employed pre- and during flight are determined largely by individual preferences as well as the individual differences to susceptibility to spaceflight conditions.

It seems that the duration of flight need not be a critical factor for maximal torque-velocity performance, i.e., the maximum torque produced at 0, 60, 120, and 180 °/sec. For example, performance of one cosmonaut on a 330-day flight and two others tested after a 175-day flight were affected similarly. The performance of cosmonauts exposed to these longer flights was affected much less than that of two cosmonauts after a 160-day flight. It is interesting to note that the maximum plantarflexor torque of cosmonauts on the 160-day flight were reduced more at the higher velocities, whereas the opposite trend occurred for cosmonauts on the longer-term flights. Maximum torque-velocity test results for cosmonauts that flew for 366 days and for 175 days were similar. Some cosmonauts had higher torques after than before flight at the higher velocities, but this never occurred at 0 °/sec.

It is not clear whether previous flight experience enabled the cosmonauts to become more effective in preventing degradation of motor performance in subsequent flights. There was a marked similarity between performance capability and volume of exercise of crew members within the same flight. Generally, all crew members on a given flight followed similar exercise protocols, and were almost always ranked consecutively within or among the ranking of all the crew members tested. One interpretation for the apparent paradox of the longer the flight the better the motor performance postflight, is that the Soviets gradually gained considerable insight into the most effective countermeasures as they gained more experience and as the spaceflights became longer. It is clear, however, that one critical factor for successfully adapting to 1G following spaceflight is the nature of the exercise countermeasures used more than the duration of spaceflight.

VI. Status of Countermeasures Using Animal Models

Recent findings on rodent models of unloading-induced muscle atrophy suggest that bouts of resistance exercise involving high force output of either the concentric or isometric mode of contraction can be effective in partially blunting the atrophy process. These types of activity appear to affect pretranslational, translational, and post translational processes. In rodents, as little as 40-50 four-second high resistance contractions per training session, every other day, were effective in partially blunting approximately 50% of the atrophy response seen during hindlimb suspension. The potential impact of resistance training as a countermeasure to unloading-induced atrophy can be put into greater perspective by the fact that it takes only 8 minutes per week of resistance exercise compared to either 640 minutes per week of endurance running or 840 minutes per week of stationary standing to achieve about a 40-

50% reduction in the degree of atrophy that occurs in rodent antigravity skeletal muscle in response to hindlimb suspension .

The period between bouts of exercise also seems to affect the ability of the muscle to maintain its mass. For example, 10-min bouts of standing, very slow walking (5 m/min) or moderate running (20 m/min) on a treadmill repeated 4 times daily (a total of 40 min exercise per day) maintained a near-normal soleus mass during 7 days of suspension. In contrast, these remedial protocols had a minimal effect on the medial gastrocnemius. Climbing a one-meter grid at an 85% incline with a load equal to 50-75% of body weight attached for 8-10 repetitions, 2 or 4 times per day (~6 min of exercise per day) resulted in significant retention of both soleus and medial gastrocnemius muscle masses, although the effect on the medial gastrocnemius was somewhat variable . These data indicate that daily periods of load-bearing can be an effective means of counteracting the atrophic response to hindlimb suspension; a very small amount (as little as 6 min) of high load-bearing activity per day can significantly attenuate the suspension-associated atrophy in the soleus and, to some degree in the medial gastrocnemius. In addition, it also appears that short, intermittent bouts of exercise interspersed throughout the day may be a more efficient countermeasure than a single long bout of exercise. Booth and co-workers speculate that intermittent bouts of exercise maintain protein synthesis at control levels during periods of unweighting.

Kirby et al. used electrically-induced (0.2 trains/sec; stimulation rate of 60 Hz; pulse duration of 0.5 sec with 16 V administered via intramuscular electrodes in anesthetized rats) maximal lengthening contractions [0.2 fiber lengths/sec over the full range (128°) of ankle excursion] of the rat soleus to counteract the suspension-induced atrophy. One leg in each rat performed 4 sets of 6 repetitions of eccentric contractions every other day during a 10-day suspension period. The contralateral leg served as the control. The soleus muscles subjected to lengthening contractions had significantly larger wet weights (30%) and noncollagenous protein contents (20%) than the contralateral control muscles. However, the attenuation of the decreases in muscle wet weight and noncollagenous proteins produced by the eccentric exercise regime was ~77 and 44%, respectively, when compared to control values from weight-bearing rats. These data further demonstrate that total time of muscle activation may not be the critical factor for countermeasure effectiveness since muscle activation utilized only 0.035% of the total non-weight-bearing time. However, Kirby et al. emphasized that, similar to all other exercise protocols used to date, this eccentric exercise regime was effective in attenuating, but not completely preventing the atrophic response of the soleus.

An interesting modification of the suspension model has been developed by Stump et al. in which one limb is placed on a platform with the leg in a position similar to that observed during standing posture. This platform provides a base against which the animal can contract or stretch the supported limb at any time during suspension. Although there has been no quantification of the amount and pattern of activation of the muscles in the supported limb, it seems logical (based on chronic EMG recordings from suspended rats) that these muscles will be producing combinations of isometric, concentric and even eccentric contractions when there is cocontraction of agonists and antagonists as the leg is extended and flexed against the platform. In addition, chronic vertical forces of ~10% body weight appear to be transmitted to the platform, indicating that weight bearing is occurring (Stump et al., unpublished observations). Muscle mass: body weight ratios of the soleus, plantaris, and gastrocnemius muscles in the supported leg were similar to cage controls after 10 days of suspension, whereas those of the freely hanging leg were significantly decreased. In contrast, the responses of the tibialis anterior and extensor digitorum were similar in the supported and unsupported legs. These data suggest that chronic low-intensity forces may be effective in preventing atrophy in those muscles that are recruited. Thus, some

progress has been made toward specifying the appropriate types, durations, and intervals of neuromuscular activity required to maintain muscle properties in chronic, unloaded conditions.

Chronic passive stretch of unloaded muscles can be effective in ameliorating some of the atrophy associated with suspension. Jaspers et al. compared the atrophic response in several ankle extensors and flexors in rats suspended for 6 days with one leg moving freely and one leg immobilized with the ankle in a dorsiflexed position. Compared to the freely moving limb, the weights of the soleus, gastrocnemius, and plantaris were 106, 20 and 7% larger, respectively, in the immobilized leg. In this light, Goldspink et al. have demonstrated a significant decrease in the DNA content of the extensor digitorum longus in rats suspended with the ankle fixed in dorsiflexion. Interestingly, Jaspers et al. reported no difference in the mass of the soleus from 6-day suspended rats when comparing the casted (plantarflexed) limb with the freely-moving limb. The mass in the gastrocnemius and plantaris muscles of the limb casted (plantarflexed) was less than these muscles in the freely-moving limb. These data are consistent with the view that muscles that are activated but unloaded atrophy more rapidly than inactive-loaded muscles. For example, it is clear that there is considerable activity in the muscles of suspended rats. It is important to note that studies in which the ankle joint is fixed in an extreme dorsiflexed or plantarflexed position the changes in muscle mass reflect changes in muscle fiber length and/or cross-sectional area. Thus, the physiological consequences of these effects on muscle mass are unclear. In addition, these effects may be short-lived since sarcomeres can be added or deleted within a few days.

Sancesario et al. used elastic bands to passively hold the ankles of one group of suspended rabbits in a dorsiflexed position and compared the effects with another group in which the ankle was allowed to hang free and assumed a plantarflexed position. Based on visual observations, the rabbits occasionally contracted both limbs physically. After 1 or 2 weeks the soleus was significantly smaller in the animals that did not have elastic bands but not in those having elastic bands at the ankle. Thus the chronic passive and/or occasional phasic loaded contractions ameliorated the atrophic response. The authors suggested that a similar device could be attached to the feet of astronauts and serve as very simple and effective countermeasure for spaceflight-induced atrophy. This approach in principle is similar to the "penguin suit", which provides resistance to movement of the legs, arms and trunk, worn regularly by cosmonauts on the Mir space station.

Other procedures could be as effective as exercise or chronic passive stretch (resistance) for ameliorating the atrophic response to unweighting. For example, centrifugation (acceleration) could be used to produce an artificially-induced gravity and thus theoretically result in an increased load on the muscles unless strategic behavioral adjustments are used to avoid the additional imposed force. D'Aunno et al. studied the effects of centrifugation at 1.5 and 2.6G for 1 or 2 hours per day on the soleus muscles of 7-day hindlimb suspended rats. Centrifugation resulted in some attenuation of the muscle atrophy for each combination of duration and intensity. There was no difference, however, between centrifugation at 1.5 or 2.6 G for either duration. In contrast, two hours of centrifugation at 1.5 or 2.6G was more effective than one hour at the same intensities. Thus, it appeared that the duration of centrifugation was more important than the intensity with respect to amelioration of suspension-induced atrophy. Interestingly, 2 hours of ground weight-support was as effective as centrifugation in preventing atrophy. In a subsequent study, D'Aunno et al. centrifuged one group of rats at 1.2G for four 15-min periods evenly spaced over a 12-hour interval during a 7-day suspension period. Another group of rats were made to weight support on the same schedule. Intermittent acceleration resulted in 42% less soleus atrophy than that in suspended-only rats, and had no effect on plantaris weight. Intermittent ground support, interestingly, had a greater effect and maintained soleus mass at 90% of control. None of the countermeasures returned muscle mass to 100% of pre-suspension control levels. The implication was that some

undefined stress associated with acceleration may have interfered with protein metabolism in the soleus and the authors indicate that more studies are needed to determine the efficacy of this potential countermeasure. In any case, it appears that the key to using chronic centrifugation in rats as a countermeasure is to assume that the G-forces imposed on the body are being transmitted via the leg musculature in a standing or walking posture. Otherwise, the presumed increased forces will be ineffective for the leg musculature. Thus, when using animal models, close attention must be given to the behavior of the animals during the experiment. In a recent 2-week centrifugation study conducted at Ames Research Center, videotaped records indicated that the rats were quite immobile during the initial 2-3 days of centrifugation, and then began to move to get food and water (M. Vasques and R. Grindeland, personal communication).

In summary, a variety of countermeasures have been used in an attempt to prevent the skeletal muscle atrophy associated with chronic unloading. Based on these results it appears that: 1) short bouts of high-intensity exercise (e.g., climbing a ladder carrying a load for a few min/day) are as effective as long bouts of low-intensity exercise (e.g., treadmill running for up to 2 hours/day) in ameliorating the atrophy of the soleus muscle; 2) multiple bouts of exercise per day are more effective than a single bout of the same intensity and total duration; 3) high-intensity exercise is required to recruit the fast muscle motor pools and thus ameliorate the atrophy in fast extensor muscles; 4) the anabolic effects of growth hormone on unloaded limbs are potentiated by high-intensity exercise, such that the soleus mass is maintained at control levels during hindlimb suspension; 5) centrifugation (duration being more critical than intensity) has some potential in ameliorating atrophy in limb muscles if the animals support their weight (stand) during the acceleration phase; and 6) chronic passive stretch helps to maintain muscle mass during unloading, with some combination of fiber cross-sectional area and fiber length being affected. Some areas which should be pursued include the following: 1) the potential of eccentric exercise (lengthening contractions) on the maintenance of muscle mass and 2) the relationship between muscle activity (amounts and patterns of loading and activation) and hormonal status, particularly growth hormone and thyroxine. Eventually these countermeasure protocols must consider all aspects of the homeostatic balance of the individual.

VIII. Recommendations

A. Specific to the Countermeasure Strategic Plan

- 1) High resistant training paradigms, aimed at eliciting maximal force production of the major muscle groups supporting posture and locomotion, need to be initiated as soon as possible as an integral strategy for maintaining the skeletal muscle system. As an initial approach, strategies similar to those currently used to optimize strength and enhance muscle enlargement in an 1G environment should be used at the outset of such a program.
- 2) NASA Life Sciences and Operational Medical Programs should explore the utilization of currently available equipment that may be capable of meeting the needs of such an exercise program, rather than looking to build new equipment devices.
- 3) Exercises that are highly repetitive and require low forces, i.e., the endurance type, should be continued as part of a general conditioning regimen.

4) Further, activities which facilitate the maintenance of routine daily neuromotor skills involved in posture, balance and vestibular control also need to be incorporated as part of the training program.

5) NASA needs to assess the level of physical skills (strength, power, endurance, motor control etc.) necessary to perform emergency egress activities that are likely to be encountered by astronauts. These levels of skill and performance capacity should serve as the guideline(s) for establishing the level of fitness to be maintained by the exercise programs used in the countermeasures program. It seems reasonable to expect that all training programs will not maintain individuals at their respective pre-flight physical capacity, and thus more reasonable performance objectives need to be identified.

6) Long term goals of NASA, in conjunction with the Exercise Countermeasures Program at JSC, need to focus studies toward basic and applied research that identifies the mechanisms of muscle wasting and motor control and to seek more effective countermeasures for preserving an acceptable level of movement performance. Research in this area should focus on strategies for increasing the efficacy of physical activity. These studies should consider interactions of physical activity, pharmacological and hormonal/growth factor approaches to understanding the regulatory elements of neuromuscular plasticity.

B. Specific to Future Research Directions and Strategies

It is apparent from both human and animal experiments, i.e., studies seeking information on countermeasures to the deficits in muscle properties, that the conventional modes of physical activity routinely used in spaceflight (treadmill, cycling, rowing, and the use special suits to impose tension on muscle) are not successful in preventing the degree of atrophy and dysfunction that occurs following several weeks of exposure to weightlessness environments.

Future research needs to focus in greater depth on the mechanisms and processes whereby muscle protein turnover is regulated. This research should clearly involve studies that target both the processes of protein synthesis and protein degradation, because it is the balance of these two processes that determines the steady state level of muscle mass. Further, since changes in MHC phenotype (as well as other contractile components) also exert a profound impact on the functional properties of the muscle, future work must focus on better understanding the role of hormonal and activity-related signals, second messenger pathways, and the transcriptional factors involved in contractile protein gene regulation. Finally, exercise studies should more clearly define the type, patterns and amount of mechanical loading (in conjunction with the use of growth factors and hormones) necessary for maintaining muscle mass, contractile protein phenotype, and the sensory-motor properties of the musculoskeletal system.

Given today's understanding of some of the fundamental principles of motor unit function and adaptation, experiments can test the appropriateness of exercise apparatuses and protocols to be used during spaceflight. This choice relates to 1) which muscle groups will be exercised and 2) what load patterns will be imposed by the muscle action. Once the recruitment level and load are defined, then the velocity is determined; or once the recruitment level and velocity are defined, then the load is determined. As noted previously, the major issues are what load-velocity combinations are the most efficacious in sustaining normal muscle properties, and how often do these specific load-velocity events have to occur? Similar questions would pertain to maintenance of normal neural control of movement and to maintenance of some defined level of resistance to a decrement in neuromuscular performance, cardiovascular performance, etc. The combined effects of all countermeasures designed for each

specific tissue must be considered in optimizing the performance of humans in space and upon return to 1G.

In examining the recent technological advances in creating an artificial form of gravity, there are several prototypes that have been designed and partially tested that have the potential to both vary g-forces on muscle and bone, exert an aerobic exercise stimulus on the circulatory system, as well as exert a positive impact on other systems (i.e., vestibular) as well. This area needs to be explored more fully as artificial gravity may have the greatest potential for maintaining in the most appropriate state for 1G .

Whether or not artificial gravity becomes a prioritized countermeasure strategy, it may be necessary to undertake more basic research, beginning first on animals models, in which mechanical activity, chiefly of the high resistance type, is interacted with hormonal and other pharmacological agents in efforts to optimize the homeostatic state of muscle, bone and connective tissue for 1G . Although our present understanding of the mechanisms of neuromuscular and musculoskeletal adaptations made not be sufficient to pinpoint the optimal exercise protocol for spaceflight, there are sufficient data to serve as a theoretical basis for conducting clinical trials. From these clinical trials it is highly likely that significant improvements could be realized with respect to the effectiveness and efficaciousness of the exercise protocols to be followed during spaceflight.

An important challenge for future studies will be to design flight experiments that will permit (1) dissociation of the effects of microgravity from those of the countermeasures, and (2) identification of the effects of flight on the neuromotor system distinct from the compensatory processes used to perform motor tasks upon return to 1G.

Success in developing an optimized battery of exercise-based countermeasures is an ultimate challenge for integrative physiology requiring the utilization of biological principles ranging from the molecular control of protein maintenance to the psychological factors that will determine whether or not a crew member chooses to utilize the countermeasure. Given the data from spaceflight and those from motor control studies from ground-based simulation studies, some conclusions and suggested general principles to develop and validate countermeasures for these motor deficits are as follows:

1) A combination of exercise modes is likely to be the most effective with each type of exercise inducing specific effects on specific muscle groups and even specific types of muscle fibers within a muscle or muscle group. It does not seem reasonable from a physiological viewpoint to assume that one specific exercise protocol would be sufficient to counteract all of the effects of spaceflight, not even for the neuromuscular system alone.

2) It appears that the execution of appropriate forces accurately and timely in a 1G environment immediately following prolonged spaceflight has a major impact on the success of a mission. Thus, careful analyses must define which components of the neuromotor system adapt and deadapt to microgravity, determine the temporal sequence and amplitude of those adaptations, and then define the mechanisms by which they are induced.

3) It is essential that baseline exercise levels and activity patterns at 1G and during spaceflight be defined for critical muscle groups. These data then can be used to determine the appropriate type and amount of neuromuscular activity that must be imposed on the baseline activity during spaceflight to reach levels comparable to that found at 1G. Based on limited data, the required amount and pattern of activity necessary to maintain the neuromotor system during spaceflight appear to be muscle and muscle fiber specific and to be somewhat unique for each individual. This individual uniqueness may reflect genetic factors as well as the physiological state of the neuromuscular system at the beginning of spaceflight.

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APPENDIX C

BONE AND CONNECTIVE TISSUE DISCIPLINE - SUPPORTING MATERIAL

Supplementary reports

C-1. Diet and Acid-Base Balance by Martin J. Fettman

C-2. Role of vitamin D and Parathyroid Hormone in Microgravity-Induced Bone Loss by Michael Holick

Report C-1
Diet and Acid-Base Balance
by Martin J. Fettman

Many factors in space flight may affect calcium metabolism and bone turnover, beyond the effects of microgravity and changes in physical loading forces. Prior physical fitness may influence remodeling forces. Caloric balance influences the amount of energy available for anabolic processes, including bone matrix synthesis. Nitrogen balance reflects the quantity of amino acids retained which may be used for bone matrix synthesis. Finally, dietary calcium balance will affect the bone mineral density. It is important to note that "balance" is used to describe diet-related factors, rather than "intake". Many processes may affect "nutrient partitioning" so that alterations in balance diverge from those of dietary intake. In space flight, one example is that of dietary protein, nitrogen balance, and differential protein synthesis. Even during periods of decreased overall nitrogen balance, inflammatory cytokine release and hepatic acute phase protein synthesis may be increased, reflecting partitioning of amino acid metabolism (Stein et al, 1993; Stein and Schluter, 1994). Likewise, it is possible to modify mineral distribution through changes in dietary electrolyte composition and influences of acid-base metabolism.

Both respiratory acidosis (increased $p\text{CO}_2$) and metabolic acidosis (decreased HCO_3) have been shown to alter bone surface mineralization through physicochemical effects defined by the solubility product relationship between ionized calcium and phosphate (Bushinsky et al, 1992 Arnett et al, 1994). The precipitation of ionized calcium and phosphate is determined both by their concentrations and that of hydrogen ions ($[\text{Ca}^{2+}][\text{P}_i]/[\text{H}^+] = K$).

This principle has been exploited in veterinary medicine to manage particular animal disorders. For instance, dietary alkalization has been used to improve eggshell quality in poultry (Keshavarz, 1994). Dietary acidification has been used to improve bone calcium mobilization in dairy cows during their "dry" period just prior to parturition (Oetzel et al, 1991). This, in turn, protects against hypocalcemia developing subsequent to the onset of lactation. Likewise, both dietary acidification and alkalization affects the urinary pH and subsequent predisposition to urolithiasis in cats (Thumchai et al, 1996). Dietary acidification prevents struvite stone precipitation, but predisposes to calcium oxalate precipitation.

Metabolic acidosis has also been shown to alter bone remodeling through cellular effects. Decreased bicarbonate concentrations reduce osteoblast activity, and stimulate osteoclast activity, in addition to the physicochemical effects noted above (Krieger et al, 1992; Bushinsky et al, 1995). There is controversy in the literature regarding the relative "potency" of respiratory vs. metabolic acidosis in altering bone mineral deposition (Sprague et al, 1994; Arnett et al, 1994). Thus, we may have cause for concern about excursions in atmospheric $p\text{CO}_2$ in the Space Station.

Acidosis has also been shown to alter the synthesis, release, and effectiveness of the calciotropic hormones (Ching et al, 1989). Acidosis increases the ionization of calcium, and increased ionized calcium concentrations in turn suppress the release of parathormone (PTH) from the parathyroid glands. On the other hand acidosis promotes the activity of PTH on bone mineral resorption. Acidosis also decreases PTH activity in the kidneys, resulting in decreased calcium reabsorption from the tubular fluid. Finally, acidosis decreases renal 1 α -hydroxylase activity, thereby reducing the production of active calcitriol.

It has been hypothesized that the usual daily load of acid produced through metabolism might have similar effects on calcium metabolism and bone turnover, even in the absence of overt disturbances in acid-base balance. Daily oral intake of KHCO_3 (but, not NaHCO_3) to neutralize endogenous acid production significantly improves calcium balance, reduces bone resorption, and increases bone formation in healthy adult males (Lemann et al, 1989) and in post-menopausal females (Sebastian et al, 1994). In addition, it is possible that in space flight, during periods of negative caloric and/or nitrogen

balance, increased endogenous acid generated by accelerated rates of catabolism may also contribute to negative calcium balance.

Increased dietary sodium intake increases the filtered renal load of sodium for excretion. This, in turn, decreases renal tubular calcium reabsorption and increases urinary calcium excretion. Some have suggested that the sodium effect may be dependent on physical fitness and activity level (Navidi et al, 1995). Dietary sodium restriction has been shown to improve calcium balance in rats (Navidi et al, 1995) and in humans (Arnaud et al, 1996). but its effects on bone mineral density have not been confirmed.

Dietary sodium restriction may have other advantageous effects as well. In rats, sodium restriction increases renin-angiotensin-aldosterone responsiveness to subsequent salt repletion and volume expansion (Wilke et al, 1995). This may be useful for preconditioning astronauts prior to administration of volume expansion countermeasures for orthostasis.

Dietary alkalization with potassium citrate, coupled with sodium restriction, has been shown to decrease the risk for urinary calcium oxalate precipitation (Goldfarb, 1988). Thus, an additional benefit of dietary modification as described above might be reduced risk for urolithiasis.

Dietary alkalization and potassium supplementation have been shown to increase nitrogen balance in some diseases (Gourgeon-Reybourm et al, 1991; Papadoyannakis et al, 1984). In additional benefit of dietary modification as described above might be moderation of reduced or negative nitrogen balance observed during some phases of space flight (Stein et al, 1993). This might also improve calcium balance as affected by endogenous acid produced through catabolism.

Quantitative dietary intake data for astronauts are limited, but indicate significant balances which may affect calcium metabolism and bone turnover. Caloric intake in 13 astronauts (8.76 ± 2.26 Mj/day) appears to be significantly less than estimated energy expenditure (11.70 ± 1.89 Mj/day) (Lane et al, 1997). This would be expected to adversely affect anabolic processes integral to bone remodeling, as well as net acid excretion and calcium balance. Sodium intake in 21 astronauts was 4116.6 ± 883.1 mg/day (Lane, 1996), well above that recommended to moderate urinary calcium excretion. This amount might also adversely affect humoral vascular responsiveness to salt and water loading in astronauts prior to return to Earth. Calcium intake (855.4 ± 220.0 mg/day) was very close to the recommended daily intake, and should not require major modification. It might be useful to calculate dietary cation-anion balance for comparison to urinary pH and titratable acid excretion in order to determine potential effects of supplemental dietary alkalization on net acid excretion and calcium balance. While changes in blood gas parameters have not been observed in limited studies to date (Whitson, 1996), increased urinary calcium and sulfate losses (Whitson et al, 1993) may reflect increases in net acid excretion which could be moderated by dietary alkalization.

Remaining questions include the following:

1. Are there thresholds for the dietary effects described above?
2. What are the changes in acid-base metabolism in microgravity? This should include not only overt changes in blood gas parameters, but also changes in urinary net acid elimination.
3. Is a lower sodium diet practicable for space flight This would include formulation of lower sodium foods, as well as concomitant modifications to maintain palatability and intake.
4. Is dietary buffer supplementation possible? This would require knowledge of the typical dietary cation-anion balance (potential dietary acidity) and effects modifications on palatability and intake.

Report C-2
Role of vitamin D and Parathyroid Hormone
in Microgravity-Induced Bone Loss
by Michael Holick

Introduction

Vitamin D and parathyroid hormone play important roles in bone metabolism. Therefore, any alteration in vitamin D and parathyroid hormone can potentially alter calcium metabolism, and have significant physiologic and pathologic consequences. Vitamin D must be metabolized in the liver to 25-hydroxy vitamin D (25-OH-D) which, in turn is metabolized in the kidney to 1,25-dihydroxyvitamin D ($1,25(\text{OH})_2\text{D}_3$). It is now recognized that $1,25(\text{OH})_2\text{D}_3$ is the biologically active form of vitamin D which is critically important for regulating the efficiency of intestinal calcium absorption. Monocytic precursor cells in the bone marrow possess receptors for ($1,25(\text{OH})_2\text{D}_3$) (VDR) and are induced to mature, into osteoclasts by ($1,25(\text{OH})_2\text{D}_3$). There is evidence to suggest that mature osteoclasts lose their VDR, and therefore, are no longer responsive to $1,25(\text{OH})_2\text{D}$ although recent evidence suggest that this may not necessarily be true. Mature osteoblasts also possess VDR and respond to $1,25(\text{OH})_2\text{D}$ by increasing the production of osteocalcin, osteopontin, and alkaline phosphatase. $1,25(\text{OH})_2\text{D}_3$ also regulates phosphorus metabolism by increasing intestinal phosphorus absorption especially in the lower small intestine.

Parathyroid hormone has a multitude of physiologic activities on both calcium and phosphorus metabolism. Parathyroid hormone enhances the tubular reabsorption of calcium in the proximal and distal convoluted tubules in the kidney. It also causes a phosphaturic effect. In the bone, monocytic precursor cells have receptors for PTH. PTH induces these cells to become mature osteoclasts. Once mature, the osteoclasts lose their receptor for PTH, and therefore, are no longer responsive to this hormone. Osteoblasts have receptors for PTH and there is strong evidence that PTH has an anabolic effect on bone especially on trabecular bone. PTH also can enhance intestinal calcium absorption indirectly and alter bone metabolism indirectly by its action on stimulating the renal production of $1,25(\text{OH})_2\text{D}$.

Effect of Bed Rest Microgravity on the Vitamin D and PTH Axis.

A review of the literature from bed rest studies and from microgravity studies have suggested that once the bone is unloaded, there is an increase in the mobilization of calcium stores. This mobilization causes a slight rise in serum ionized calcium concentrations which, in turn, decreases the synthesis and secretion of PTH. The decrease in blood levels of PTH has a variety of physiologic effects. Most importantly, a decrease in the serum levels of PTH causes an increase loss of calcium into the urine. This can potentially increase the risk of developing kidney stones. The decrease in PTH may also decrease osteoblastic activity and therefore, bone formation. Since PTH also regulates phosphorus metabolism in the kidney; it is possible that the depressed production of PTH could lead to a small increase in fasting blood levels of serum phosphorus. PTH also indirectly regulates intestinal calcium absorption by regulating the renal production of $1,25(\text{OH})_2\text{D}$. Therefore, when the blood levels of PTH are suppressed, there is a decrease in the metabolism of 25-OH-D to $1,25(\text{OH})_2\text{D}$. This results in a decrease in intestinal calcium absorption

Therefore, a vicious cycle is established when the skeleton is unloaded, i.e., the body appears to depend on the bone for its major source of calcium since there is a significant decrease in intestinal calcium absorption presumably because of the decrease synthesis of $1,25(\text{OH})_2\text{D}$. Therefore, when

considering the calcium intake for astronauts, this issue needs to be carefully considered. Although it is reasonable for astronauts have an adequate amount of calcium in their diet, i.e., 800 to 1000 mg, it is probably not appropriate to substantially increase this level much beyond this. The reason for this is that since the efficiency of intestinal calcium absorption is relatively low, the increase of calcium that remains in the intestine and ultimately evacuated in the stool could potentially alter gastrointestinal motility and cause constipation. It is unclear at this time whether the use of $1,25(\text{OH})_2\text{D}_3$ to enhance the efficiency of intestinal calcium absorption would be wise. The reason for this is that $1,25(\text{OH})_2\text{D}_3$ will definitely enhance intestinal calcium absorption. However, if bone formation is significantly decreased and cannot use this calcium, the increased absorption of calcium into the blood can ultimately increase calcium and the risk of kidney stones, hypercalcemia and soft tissue calcifications.

How Much Vitamin D is Required and what Should the Source of Vitamin D for Astronauts?

Most vitamin D for humans comes from exposure to sunlight. However, on the Shuttle and in the Space Station, the astronauts will not be exposed to any sunlight that could produce vitamin in their skin. Although the RDA for vitamin D in adults is 200 IU/day, there is evidence from our submarine study that suggests that in the absence of any exposure to sunlight, the RDA should be closer to 600 IU/day. Thus, a multivitamin that contains 400 to 600 of vitamin D should be adequate to maintain vitamin D stores in astronauts especially when on long duration flights.

An alternative method to provide, in a passive manner, vitamin D to astronauts is to incorporate into the lighting system a source of simulated sunlight that contains a small amount of ultraviolet B radiation. For example, a simulated sunlight source could be provided in a small area that is used as an active area. There is mounting evidence that exposure to ultraviolet radiation may have some beneficial effects for the body that not only includes the production of vitamin D, but also the feeling of well being due to the production of b-endorphins.

Conclusion

There is no question that microgravity-induced bone loss continues to be a significant physiologic adaptation that can have detrimental short-term and potentially long-term effects on astronauts. Therefore, there continues to be a need to better understand the mechanisms involved in microgravity-induced loss and to develop counter measures to prevent it. From a hormonal point of view, there is strong evidence to suggest that the mobilization of calcium from the skeleton alters the PTH vitamin D axis. This ultimately results in a decrease in intestinal calcium absorption and the continual removal of calcium from the bone to satisfy the body's calcium requirement for its metabolic functions. It is important that the astronauts have an adequate dietary source of calcium probably in the range of 800 to 1000 mg/day along with an adequate source of vitamin D that approaches 600 IU/day. Consideration should be given to the incorporation of a simulated sunlight source for long-duration space flight as a mechanism to passively provide astronauts with their vitamin D requirement. The solar simulated light source may also provide them with other benefits as well including a feeling of well being.

There are a variety of other hormones that certainly can impact on both calcium and bone metabolism. Most notably, glucocorticoids can significantly alter calcium and bone metabolism. There is strong evidence to suggest that serum cortisol levels are increased in astronauts especially during the early part of their flight. Whether this is due to the stress of the flight or other causes is unclear at this time. There may be other hormonal factors such as IGF and its binding proteins that could be altered in microgravity and this requires further investigation.

C-3 - Additional Material

Excerpts of recommendations from other countermeasures groups

1. Musculoskeletal Adaptations to Weightlessness and Development of Effective Countermeasures. *Med. Sci. Sports Exerc.*, Vol. 10, pp. 1247-1253, 1996.
2. Medical Policies and Requirements Document. Prepared by Medical Policy Board, Revision Three, August 30, 1996.
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Musculoskeletal Adaptations to Weightlessness and Development of Effective Countermeasures

Med. Sci. Sports Exerc., Vol. 10, pp. 1247-1253, 1996

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ABSTRACT

A Research Roundtable, organized by ACSM with sponsorship from NASA, met in November 1995 to define research strategies for effective exercise countermeasures to weightlessness. Exercise was considered both independently of, and in conjunction with, other therapeutic modalities (e.g., pharmacological, nutritional, hormonal and growth-related factors) that could prevent or minimize the structural and functional deficits involving skeletal muscle and bone in response to chronic exposure to weightlessness, as well as return to earth baseline function if a degree of loss is inevitable. Musculoskeletal deficits and countermeasures are described with respect to: 1) muscle and connective tissue atrophy and localized bone loss; 2) reductions in motor performance; 3) potential proneness to injury of hard and soft tissues; and 4) probable interaction between muscle atrophy and cardiovascular alterations that contribute to the postural hypotension observed immediately upon return from space flight. In spite of a variety of countermeasure protocols utilized previously involving largely endurance types of exercise, there is presently no activity-specific countermeasure(s) that adequately prevent or reduce musculoskeletal deficiencies. It seems apparent that countermeasure exercises that have a great resistance element, as compared to endurance activities, may prove beneficial to the musculoskeletal system. Many questions remain for scientific investigation to identify efficacious countermeasure protocols, which will be imperative with the emerging era of long-term space flight.

INTRODUCTION

For several decades both human beings and laboratory animals have been exposed to the environment of weightlessness associated with space flight. During this time, a large body of evidence has been gathered to clearly show that exposure to such an environment of varying duration--days to weeks to months--results in structural and functional deficits in the musculoskeletal system.

These deficits could affect muscular function during space flight, particularly in activities requiring high precision and muscular force--such as is the case during extravehicular activity. However, the decrements become more significantly expressed as astronauts return to a partial-G or 1 G environment. These deficits could have catastrophic consequences, for example if the need arose for emergency egress upon return to a 1G environment. The deficits also affect motor abilities requiring even modest amounts of strength, endurance, and coordination, such as required for locomotion. If the deficits in bone mass and strength are not restored after return to 1 G, then they may also have long-range consequences by increasing the risk of fracture with aging.

A Research Roundtable was organized by the American College of Sports Medicine (ACSM) with sponsorship from the National Aeronautics and Space Administration (NASA). The Roundtable met at the National Center of ACSM on November 7 and 8, 1995. The goal of this Roundtable was to define research strategies for exercise, both independently of and in conjunction with other therapeutic modalities (e.g., pharmacological, nutritional, hormonal and growth-related factors) that could prevent or minimize the structural and functional deficits involving the skeletal muscle and bone in response to chronic exposure to weightlessness, as well as return to earth baseline function if some degree of loss is inevitable.

BACKGROUND

The driving force behind a Roundtable specifically focusing on the integrative theme of weightlessness, exercise, and the musculoskeletal system stems from an evolving data base derived from both biological and biomedical ground-based and space-related research. These data strongly suggest that in spite of a variety of countermeasure protocols being utilized that involve largely aerobic types of exercise (in which exercise is performed with a bias to many muscular contractions against relatively low loads), there is presently no activity-specific countermeasure that adequately prevents or reduces identified deficiencies in the musculoskeletal system.

The musculoskeletal deficits include, but are not limited to, the following: 1) muscle and connective tissue atrophy and localized bone loss; 2) reductions in motor performance; 3) potential proneness to injury involving both hard and soft tissues; and 4) probable interaction between muscle atrophy processes and cardiovascular alterations that collectively contribute to the postural hypotension observed upon immediate return from space flight.

Because NASA is entering into a new era of long-term space flight, the deficits in musculoskeletal structure and function that were tolerable to some degree with shorter flights, become intolerable with flights that extend months or years. It seems apparent that countermeasure exercises that have a greater resistance element when compared to endurance activities, may prove beneficial to the structure and function of skeletal muscle and bone.

The Roundtable was structured to involve leading researchers in the related fields of muscle and bone biology, biomechanics, exercise physiology, and clinical medicine. These individuals reviewed and discussed currently available information on what is known and unknown concerning musculoskeletal plasticity and function in response to interventions such as: 1) different types of physical activity of varying intensity, duration, and frequency; 2) exposure to space flight of varying duration; and 3) ground-based models designed to simulate weightlessness such as immobilization, water immersion, bed rest, and limb suspension. The review of information included analyses of both human and animal models.

As a result of these deliberations, the Roundtable participants identified a number of key observations that were coupled to a series of recommendations, both general and specific. The recommendations are intended to guide future research on musculoskeletal structure and function in the context of states of unloading, and for the development of effective countermeasures. These recommendations are aimed at both basic and directed research involving both humans and research animals, with the ultimate objective of preserving the functional integrity of not only the musculoskeletal system, but other physiological systems also heavily impacted by chronic exposure to states of weightlessness.

Moreover, the Roundtable participants were cognizant of the fact that information gained from such a research focus would have a tremendous impact on aging and a variety of health problems associated with physical inactivity, debilitating diseases and injury, and rehabilitation.

OBSERVATIONS AND RECOMMENDATIONS

I. OVERVIEW OF ISSUES CONCERNING FUTURE RESEARCH DIRECTIONS

I-A. Observations:

1) Based on the data analyzed by the Roundtable participants, it is apparent that exercise protocols of the endurance type (i.e., cycling, simulated running, rowing, etc.) that are currently used in space flight missions of varying duration to counteract a variety of cardiovascular deficits (and likely other systems as well), are insufficient for the musculoskeletal system and do not fully maintain normal motor control of posture and locomotion, muscle and bone mass, and regulatory processes that prevent postural hypotension. These deficits both individually and collectively could potentially impair the performance of a variety of tasks carried out during space flight (e.g., extravehicular activity) and upon landing in either 1 G or partial G environments.

2) Available information further suggests that a single uniform exercise protocol is likely to be insufficient to fully maintain the structural and functional integrity of those systems impacting motor activity, musculoskeletal function, and circulatory homeostasis.

I-A Recommendations:

1) A broad-based research plan must evolve with an overall strategy of designing a battery of exercise countermeasures aimed at preserving integrated physiological processes necessary for maintaining total body homeostasis during both space flight and upon return to a partial-G or 1 G environment. While the Roundtable participants focused more specifically on the musculoskeletal system, it recognized the importance of the interactions with other systems as well, e.g., the cardiovascular system and particularly its peripheral vascular control.

2) A minimum of four types of activity paradigms should be developed and configured for the space environment that will likely be experienced on either the shuttle and/or space station. These paradigms are defined herein relative to the desired performance outcomes. a) Routine motor skills (tasks) suitable for maintaining posture and basic locomotor function. Motor control tasks should be designed for both the upper (trunk) and lower body. Preferably this activity paradigm should be developed in conjunction with equipment or devices that could restore partial gravity forces on the body. b) Heavy resistance paradigms, involving isometric, concentric, and eccentric muscular actions, should be designed to optimally load the lower extremity and trunk musculature to maintain a positive protein balance in these muscle groups. c) Activities that generate either a high impact or produce sufficient strain on bone to maintain its structure and mineral density also need to be developed. Where possible, activities that create simultaneous maintenance of the above properties of both bone and muscle should be prioritized. d) An element of aerobic activity should be included in the training regimens with the primary objective of maintaining cardiovascular function and homeostasis, e.g., plasma volume. In all preventive and therapeutic activity paradigms, attention should be paid to the incidence of, and proneness for, injury to soft and hard tissues, and short- and long-term consequences of such injury should be determined.

3) Because time available for the astronaut corps that is dedicated to exercise is such a premium, it is apparent that in order to seek more economical exercise counter measure strategies, research should be undertaken to explore other interventions (pharmacological, hormonal, and growth factors) that could independently or in conjunction with exercise stimuli maintain musculoskeletal structure and function.

4) Future research should incorporate both basic (mechanistic) and directed research programs that utilize both animal and human models in addition to the experimental resources that will be available on the space station. Experiments should be designed around acceptable models of unloading such as bed rest and unilateral lower extremity suspension for humans and the hindlimb suspension model for animals (rodents).

VI. OBSERVATIONS AND RECOMMENDATIONS ON BONE

VI-A Observation:

When the skeleton is unloaded as in space flight, bone mass is lost in weightlessness. This bone loss is more localized than originally predicted and shows individual variation, ranging from none to 10.1% of preflight values in the spine, 1.3 to 11.4% in the femoral neck, and 0.4 to 9.5% in the tibia bone of Cosmonauts after long-duration flights. The bone loss associated with microgravity can be accelerated by age-related bone loss and changes in reproductive hormone levels and there is no evidence that the bone loss is recoverable. Potential consequences of significant bone loss include fractures on re-entry - particularly in a situation of emergency egress - and accelerated osteoporosis.

VI-A Recommendations:

- 1) Determine site specific rates and magnitudes of bone loss at 0 G and differences according to gender, age, endocrine, and nutritional status.
- 2) Determine whether individual variations in rates of bone loss are dependent upon factors such as gender, age, hormonal status, pre-flight bone status - that could be used to identify individuals at risk for excessive bone loss at 0 G and consequent risk for fracture.
- 3) Assess the efficacy of pre-flight training protocols to mitigate, skeletal loss during space flight. For example, determine if bone mass values that are substantially above the mean prior to liftoff may allow the astronaut to withstand bone loss and not be at risk for fractures. These protocols should be developed in a gender-specific manner.
- 4) Establish time and degree of bone restoration upon return to 1 G and determine its relationship to flight duration, exercise done in space, age, and gender.
- 5) Relate density variations to typical loading patterns to assess fracture risk prior to, during, and postflight.

VI-B Observation:

The endocrine system has profound effects on bone metabolism and there is evidence that space travel alters hormone secretion. Low levels of reproductive hormones (i.e., estrogen and testosterone) and high levels of corticosteroids result in bone loss, whereas increased levels of insulin-like growth factors are associated with higher bone and lean mass.

VI-B Recommendations

- 1) Define the endocrine profile in long duration space flight for men and women. Identify these changes as central or peripheral processes.
- 2) Investigate the interaction between reproductive hormones and reduced mechanical forces on bone loss in 0 G.
- 3) Determine the effect of weight-bearing exercise, which promotes muscle strength and power development, on insulin-like growth factors and bone mass. Evaluate the responses according to gender.
- 4) Evaluate the efficacy of anti-resorptive agents (e.g., bisphosphonates) on reduction in loading related, hormonal and age-related bone loss in space according to gender.

VI-C Observation:

The structural capacity of whole bones depend on bone geometry (cross-sectional area and moments of inertia) and material properties (strength and modulus) of both cortical and trabecular bone. While age-related and hypo-gravitational changes in the material properties of diaphyseal cortical bone appear to be compensated for by geometric increases in moment of inertia, material properties of trabecular bone are strong, power law functions of density. Trabecular density in turn is strongly associated with measures of trabecular morphology such as average trabecular width, spacing and connectivity. Issues of bone "quality" that may be related to weightlessness are now focusing on mineralization, collagen

content, and damage accumulation, and there is some evidence that these factors may be influenced by space flight.

VI-C Recommendations:

- 1) Develop noninvasive techniques to estimate trabecular bone strength; for example using pQCT (peripheral quantitative computed tomography), DEXA (dual energy x-ray absorptiometry), ultrasound, and MRTA (mechanical response tissue analyzer) technologies.
- 2) Use these techniques to track the strength of bone systematically from pre-flight, in-flight, post-flight and long-term recovery upon return to normal weight bearing.
- 3) Determine differences in morphology and material properties of bones remodeled in space compared with those remodeled on Earth.

VI-D Observation:

The current exercise modalities typically used during space flight are inadequate to maintain bone mass. Weight bearing activities performed at 1 G that incorporate impact loading and which increase muscle mass, power and strength (i.e., gymnastics, wrestling) also increase bone mass. In 1 G environments, running or hopping in place provide substantially higher impact loads (and thus bone strain) than do activities such as cycling, walking or resistance training exercises. In external loading animal models, thresholds for bone maintenance and increase have been shown for loading variables such as strain magnitude, strain rate, frequency (Hz), strain distribution, and number of loading repetitions.

VI-D Recommendations:

- 1) Characterize actual bone strains at clinically relevant sites in humans during specific movement patterns (including cycling, treadmill walking and running, jumping in place, and resistance training exercises), and determine the relationship of strain to age, size, and gender.
- 2) Determine mechanical loading thresholds for bone mass maintenance in adults and determine whether these protocols are specific to age, bone size or gender.
- 3) Determine exercise prescriptions and other mechanical interventions that are sufficient to maintain bone mass during weightlessness, and determine whether these protocols are specific to age, bone size or gender.
- 4) Determine the molecular and cellular signals associated with bone loss due to decreased loading as observed in disuse and weightlessness, and determine how these signals compare with signals for bone hypertrophy.
- 5) Determine to what extent the bone loss that occurs during 0 G exposure is due to the lack of mechanical load, and to what extent systemic change (e.g., fluid shifts, hormone expression) can modulate the response to unloading.

VI-E Observation:

Nutrition is important for bone health, independent of its influence on body weight. Specific nutrients, such as calcium and phosphorus, are essential components of bone crystals. In addition, there are other nutrients -- such as vitamin D, magnesium, and protein -- that are known to impact bone mass.

VI-E Recommendations:

- 1) Define the protein, mineral and energy requirements for bone maintenance.
- 2) Determine to what extent astronauts in space have adequate energy, vitamin, and mineral intake and absorption, and to what extent exercise regimens alter these needs and intakes.

VI-F Observations:

1) Experimental models for the musculoskeletal system are classically human adults who volunteer for bed rest of varying periods of time, and for upright models in which some muscles of one leg are unloaded. These models appear to be valid for space flight, but direct comparisons of many measurements from ground-based studies with those made during space-flight are lacking.

2) Small animal models currently in use for space flight experiments have generated a great deal of information on responses to 0 G and bone-muscle unloading. However, little information has been obtained on mature animal models.

VI-F Recommendations:

1) Make direct comparisons of measurements from ground-based studies with those made during space-flight.

2) Compare the responses to unloading in mature animals to those of younger animals of the same species in both ground based and in-flight experiments. Incorporate the differences in maturity for bone and muscle into experimental design (i.e. 95% of the skeleton in the male rat is acquired by 6 months of age, yet muscle experiments typically consider 4-month-old rats to be mature).

SUMMARY AND CONCLUSIONS:

Research aimed at understanding the adaptive processes of human beings in response to the environment of weightlessness is both complex and difficult to perform. This is due to the inherent problems associated with using humans as research subjects, because they must adhere to a variety of operational medical procedures, and perform a wide variety of duties during a given mission. These factors often ultimately compromise the variables being investigated thus making the interpretation of the experiments difficult. Furthermore, the availability of the microgravity environment of space travel often precludes an ideal experimental design, particularly in controlling the important variable of duration and transient high G forces on ascent and descent.

Therefore, it is essential that future research focus both on human and animal subjects that can be configured into ground-based models simulating chronic states of weightlessness in order to examine both the mechanistic and applied components of the scientific issues raised in this report.

It seems highly unlikely that a single exercise paradigm will evolve that effectively ameliorates the important structural and functional deficits occurring in bone, muscle, and connective tissue identified in this report. Thus, it is imperative that a systematic and highly integrated research strategy evolve to ensure the likelihood that a multifaceted exercise prescription is established to maintain the functional integrity of the various components of the musculoskeletal system when they are challenged by the debilitating environment of weightlessness.

MEDICAL POLICIES AND REQUIREMENTS DOCUMENT

Prepared by Medical Policy Board

Revision Three, August 30, 1996

7.0 Rationale for Selection of Monitoring and Countermeasure Modalities

Exposure to microgravity and the space environment has important medical and health implications, including bone loss (matrix and mineral), increased cancer risk, neurovestibular changes, orthostatic hypotension, etc. Because of mission costs and the risks inherent in human space flight, as well as other factors, it is imperative that crew members function at peak performance levels at all times. Clearly, based on these factors, certain minimal requirements for crew performance exist. Crew members must remain physically and mentally healthy and physiologically capable of performing all mission tasks. The flight deck crew (for U.S. Shuttle missions) must be able to maintain orthostasis and perform the critical operations required to fly the Shuttle, while sitting upright, during entry. All crew members must be capable of egressing the spacecraft unaided in an emergency. In addition, astronauts must have some degree of career longevity, with recovery, rehabilitation and repair capabilities available upon their return from space flight. For these reasons, we must be able to provide preventive measures, monitor the health of the crew both on the ground and in flight (human performance and environmental effects are evaluated periodically by monitoring both the sustained physiological changes during space flight and the spacecraft environment), provide appropriate medical care when needed, and prescribe effective countermeasures to prevent or ameliorate the debilitating effects of exposure to microgravity.

7.1 Baseline Current Knowledge and Available Countermeasures

To date, life sciences research has yielded countermeasures addressing some of the health issues listed above. Tables 1-8 and Charts 1-4 (found in Appendix 3) contain a basic outline of the current status of our knowledge of physiological changes, in flight and postflight, and available countermeasures, for those body systems of primary concern for health maintenance (i.e., those systems for which adaptation to microgravity does not necessarily present a risk to the person while in space, but can be debilitating upon return to Earth: the cardiovascular, muscular, skeletal, and neurosensory/neuromotor systems. The responses of the remainder of the body systems are not yet fully understood and research is not yet complete. A summary of prioritized research questions can be found at Appendix 4.

7.2 Developing and Applying New Countermeasures

The NASA MPB is ultimately responsible for approving what countermeasures are actually applied. This is done via the creation of Level 1 Policy Statements. Level 2 documents regarding the interpretation and application of the MPB policies, as well as Level 3 documents discussing, in detail, implementation methodologies, protocols, flight rules, etc., are the responsibility of the AMB at JSC. Appendix 5 provides a summary of what countermeasures are currently accepted and approved by the MPB and also displays those countermeasures which are under consideration but have not yet been fully validated from a scientific and clinical standpoint.

7.3 Selecting Countermeasure Protocols

1) General concepts - Planned health monitoring modalities and responses to countermeasures will be conducted at regular intervals (no more than three times), in conjunction with the physical health evaluations prior to the first mission, to establish a baseline normative data base against which postflight recovery will be implemented. During subsequent missions, depending on the clinical judgment of the

crew surgeon, only select protocols might be implemented if adequate baseline data already exists. In the postflight phase, guided by clinical manifestations and physical evaluations, only those protocols will be implemented which are required for diagnostic purposes or to guide the rehabilitation process and the return to flight duties. Hydration with an orally consumed isotonic solution, during LBNP and exercise protocols, is required to minimize orthostatic responses and reduce the risks of renal calculi.

9.0 Definition of Terms

The following definitions are provided to clarify the context within which they were developed. The adoption of clearly enunciated principles minimizes chances for misinterpretation of the requirements contained within this document.

4. Countermeasures - application of procedures and/or therapeutic means to prevent or minimize adverse health and medical events. These can be divided into the following categories:

4a. Primary Prevention - eliminating the adverse or harmful agent or preventing it from reaching the astronaut. Examples include: 1) the Crew Health Stabilization Program and immunizations, which protect against infections; 2) preflight medical exams to identify and correct risks; and 3) providing a gravitational substitute effect on orbit, preventing microgravity from degrading the health of the astronaut.

4b. Secondary Prevention - mitigating the effect of adverse or harmful agents or enhancing the astronaut's ability to ward off the harmful effects of these agents. Examples include: cabin air and water purification, exercise to counteract the microgravity effect, and fluid loading and antigravity suits to minimize orthostatic intolerance. Astronaut selection standards might also be considered a form of secondary prevention.

4c. Tertiary Prevention - to minimize the effect of adverse or harmful agents on the crew once maladaptation, disease, or injury has been identified. The postflight rehabilitation program is a good example of such restoration, hopefully leading to treatment and issuance of waiver for continued flight duties with periodic observation.

Appendix 3

Monitoring and Countermeasures Tables and Charts

BONE AND CALCIUM STATUS (Table 5)

Physiological Parameters--Hypercalcemia, hypercalciuria, altered GI absorption, skeletal architecture, altered hormone levels, back pain.

BONE AND CALCIUM COUNTERMEASURES UNDER CONSIDERATION

Hypercalcemia--fluid, diet (currently accepted practices [needs adjustments based on absorption and metabolic research information overview]) both inflight and postflight

Hypercalciuria--fluid, diet (currently accepted practices [needs adjustments based on absorption and metabolic research information overview]) both inflight and postflight

Skeletal architecture--exercise (intensive resistive exercise[requires further research into protocols and type of hardware]) inflight, rehab postflight

Back pain--posture control (intensive resistive exercise[requires further research into protocols and type of hardware]) inflight, rehab postflight

NUTRITION

Monitoring

1. Pre/postflight
 - a. Weight (body mass)
 - b. Selected hematologic and clinical chemistry studies
2. Inflight
 - a. Body mass measurement weekly
 - b. Questionnaire

Inflight diet

1. Adequate calories based on individually calculated needs
2. Adequate variety and selection of foods
3. Vitamins
4. Fiber

1. Balanced Diet
 - a. calories
 - b. fat
 - c. protein
 - d. carbohydrates
 - e. fiber

1. General metabolism
2. Food Stuff
absorption and
utilization

SKELETAL SYSTEM (BONE AND CALCIUM (Chart 3)

Monitoring (Long Duration Missions)

1. Baseline monitoring:
 - a. Two imaging studies (two years apart) to establish fast or slow type of bone loss.
2. Preflight monitoring:
 - a. Imaging to evaluate skeletal status (if indicated).
 - b. Renal stone risk profile
3. Inflight monitoring:
 - a. Non-invasive bone density measurement (ultrasound of skull and trochanter).
 - b. Body mass measurement
4. Postflight monitoring:
 - a. Imaging ASAP and as clinically indicated for follow-up.

Countermeasures

1. Rehabilitation (postflight)

NUTRITION

Monitoring (Short- and Long-Duration Missions)

1. Pre/Postflight monitoring:
 - a. Weight (body mass)
 - b. Selected hematologic and clinical chemistry studies
2. Inflight monitoring:
 - a. Body mass measurement weekly
 - b. Questionnaire

Inflight Diet

1. Adequate calories based on individually calculated needs

2. Adequate variety and selection of foods
3. Vitamins
4. Fiber

Appendix 4
Research Questions

A. Health Maintenance

Skeletal System (Bone and Calcium)

1. Appropriate exercise countermeasures for bone preservation
2. Use of medications as a countermeasure for hypercalciuria and bone loss
3. Hormonal status and space loss interactions
4. Bone/skeletal architecture
5. Mineral absorption (oral) and general metabolism

Nutrition

1. How are nutrients absorbed and metabolized?
2. What is the optimal diet composition to maintain muscle and bone mass?
3. What are the optimal vitamins and trace elements in the prevention of the adverse effects of microgravity?

B. Medical Care

Appendix 5
Categorization of Countermeasures
Operational and Research Status

SKELETAL SYSTEM (BONE AND CALCIUM)

Operational

To Be Further Refined (Research)

1. Exercise (loading)
2. Medications
3. Diet

NUTRITION

1. Balanced diet
 - a. calories
 - b. fat
 - c. protein
 - d. carbohydrates
 - e. fiber

1. General metabolism
2. Food stuff absorption and utilization

HUMAN RESEARCH FACILITY SCIENCE AND TECHNICAL REQUIREMENTS DOCUMENT

JANUARY 29, 1996

3.0 SCIENCE REQUIREMENTS

The science requirements for the HRF have been derived from the science needs of the communities listed in Subsection 3.1 and the Discipline Science Plans listed in Appendix A. There are several research objectives that are common to all disciplines and are therefore of high priority. The common objectives include

- Determine the rate, extent, and time course of the effects of exposure to microgravity on all human physiologic systems (and determine if these effects are reversible after return to Earth)
- Understand the underlying mechanisms responsible for the physiological adaptation to space flight, including any variations between gender and age groups.
- Identify the potential risks of microgravity exposure to humans for both health and performance in space and on the ground and develop effective countermeasures.
- Use microgravity and other unique characteristics of the space environment to enhance our understanding of fundamental biological processes on Earth.

3.1 DISCIPLINES ENCOMPASSED

3.1.3 Muscle, Skeletal and Connective Tissue

I. BACKGROUND

Long-term exposure to microgravity will most assuredly cause significant loss of muscle and bone unless effective countermeasures can be developed. The severity and significance of these changes are unknown at this time. The limited data obtained from the U.S. (Skylab era - 28, 56, and 84 days) and the Soviet/Russian flight experience (Soyuz/Mir flights to 15 months) do not adequately address these problems. The International Space Station (ISS) will provide flight opportunities to study the magnitudes, time courses, and mechanisms of changes in muscle, skeletal, and connective tissues and the implications for their combined system performance capabilities during long-duration flights and subsequent readaptation to 1-g.

Musculoskeletal integrity is vital to successful human performance during space flight and upon return to a 1-gravity (1-g) environment. Effective countermeasures to the changes in the musculoskeletal system that occur during prolonged space flight have not been employed to date. Thus, the determination of appropriate countermeasures is an important scientific objective in its own right. Musculoskeletal changes also affect the control of movement in fine motor tasks, control of posture, strenuous physical work (IVA and EVA), and responses that involve visual feedback, and perceptions of movements to be executed. Insight gained from changes to the musculoskeletal system in space may also have direct relevance to changes seen in 1-g as a consequence of aging, and recovery from trauma and surgery.

3.1.3.2 Connective Tissue (CT including soft CT and bone)

II. SCIENCE OBJECTIVES

1. To determine the time of adaptation of bones and tendons that have different functions and loading histories in microgravity (and upon return to 1-g).
2. To determine the in-vivo biochemical assessments of bone turnover, electrolytes, and hormones that reflect changes in connective tissue metabolism in a microgravity environment.
3. To determine the dose-response relationship between loads of different characteristics and bone mass.
4. To develop appropriate countermeasures to maintain connective tissue structure and bone mass during prolonged exposure to microgravity.

III. FUNCTIONAL REQUIREMENTS

1. Capability to accurately quantitate the loss in bone and tendon quality and mass that occurs during space flight (e.g., ultrasound, bone densitometry).
2. Capability to monitor blood and urine concentrations of proven biochemical markers of bone turnover and the electrolyte and hormonal changes that substantiate these changes.
3. Capability to collect, store, and prepare tissues inflight and return to Earth (e.g., freezer, N2, chemical fixing, centrifuge)
4. Capability to generate and measure different loading profiles to the axial and peripheral skeleton during spaceflight at rest and during exercise (e.g. LEAP, dynamometer, treadmill, bicycle).

3.1.4.3 Endocrinology and Renal Function

I. BACKGROUND

Exposure to microgravity profoundly affects fluid homeostasis. The headward shift of fluids observed in either real or simulated microgravity results in decreased volume of body fluid compartments and an apparent shift of fluid from the extracellular to intracellular compartment. Reduced fluid volume probably contributes to cardiovascular deconditioning during space flight and orthostatic intolerance after landing. The development of successful countermeasures to these, and perhaps other undesirable effects, will be based on the understanding of the sequence of physiologic events during adaptation to weightlessness and readaptation to Earth's gravity.

The physiological changes associated with space flight contribute to an altered urinary chemical environment. Inflight changes previously observed include decreased urine volume and increases in urinary calcium, phosphate, potassium and sodium excretion, all of which could potentially exaggerate the risk of renal stone formation. The formation of a renal stone could have severe health consequences for the crew member.

Description of the response of the endocrine system to space flight has come from comprehensive measurement of hormones in the blood and urine of crew before and after flight as well as during flight. However, little information has been obtained from flight or ground based investigations regarding reproductive function. In short Shuttle missions, as in 7 day bedrest studies, female reproductive hormones and their cycles do not appear to be greatly affected. The effect of more prolonged exposure is completely unknown. Therefore, for prolonged missions, reproductive regulation and function need to be addressed.

II. SCIENCE OBJECTIVES

1. Describe and understand the effects of exposure to microgravity on endocrine function. Specifically, the impacts on hormonal regulation of fluid homeostasis (including drinking behavior) and calcium bone balance are essential.

2. Determine the effects of space flight on renal function, specifically as it relates to regulation of body fluid volume.
3. Quantitate the pre-, in-, and postflight risk of renal stone formation associated with spaceflight.
4. Determine the influence of environmental factors (diet, fluid, exercise, and medication use) on the risk of renal stone formation.
5. Define and evaluate countermeasure(s) to minimize the risk of inflight renal stone formation.
6. Assess the consequences of short and long term exposure to space flight on female reproductive endocrine cycle.

III. FUNCTIONAL REQUIREMENTS

1. Capability to measure fluid compartments and renal function during space flight.
2. Capability to accurately quantitate the urinary risk factors associated with renal stone formation.
3. Capability to collect, preserve/store, and analyze blood inflight for measurement of endocrine and biochemical profiles.
4. Capability to collect, measure, aliquot, preserve/store, and analyze urine inflight. This capability should include both male and female urine collection devices.
5. Capability to monitor diet, fluid intake, exercise, and medication use by crew members during flight.

ACSM Position Stand on Osteoporosis and Exercise

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Summary

American College of Sport Medicine Position Stand on Osteoporosis and Exercise. Osteoporosis is a disease characterized by low bone mass and microarchitectural deterioration of bone tissue leading to enhanced bone fragility and a consequent increase in fracture risk. Both men and women are at risk for osteoporotic fractures. However, as osteoporosis is more common in females and more exercise-related research has been directed at reducing the risk of osteoporotic fractures in women, this Position Stand applies specifically to women. Factors that influence fracture risk include skeletal fragility, frequency and severity of falls, and tissue mass surrounding the skeleton. Prevention of osteoporotic fractures, therefore, is focused on the preservation or enhancement of the material and structural properties of bone, the prevention of falls, and the overall improvement of lean tissue mass. The load-bearing capacity of bone reflects both its material properties, such as density and modulus, and the spatial distribution of bone tissue. These features of bone strength are all developed and maintained in part by forces applied to bone during daily activities and exercise. Functional loading through physical activity exerts a positive influence on bone mass in humans. The extent of this influence and the type of programs that induce the most effective osteogenic stimulus are still uncertain. While it is well-established that a marked decrease in physical activity, as in bedrest for example, results in profound decline in bone mass, improvements in bone mass resulting from physical activity are less conclusive. Results vary according to age, hormonal status, nutrition, and exercise prescription. An apparent positive effect of activity on bone is more marked in cross-sectional studies than in prospective studies. Whether this is an example of selection bias or differences in the intensity and duration of the training programs is uncertain at this time. It has long been recognized that changes in bone mass occur more rapidly with unloading than with increased loading. Habitual inactivity results in a downward spiral in all physiologic functions. As women age, the loss of strength, flexibility, and cardiovascular fitness leads to a further decrease in activity. Eventually older individuals may find it possible to continue the types of activities that provide an adequate load-bearing stimulus to maintain bone mass. Fortunately, it appears that strength and overall fitness can be improved at any age through a carefully planned exercise program. Unless the ability of the underlying physiologic systems essential for load-bearing activity are restored, it may be difficult for many older women to maintain a level of activity essential for protecting the skeleton from further bone loss. For the very elderly or those experiencing problems with balance and gait, activities that might increase the risk of falling should be avoided. There is no evidence at the present time that exercise alone or exercise plus added calcium intake can prevent the rapid decrease in the immediate postmenopausal years.

Nevertheless, all healthy women should be encouraged to exercise regardless of whether the activity has a marked osteogenic component in order to gain the benefits that accrue from regular exercise. Based on current research, it is the position of the American College of Sports Medicine that: 1. Weight-bearing physical activity is essential for the normal development and maintenance of a healthy skeleton.

Activities that focus on increase muscle strength may also be beneficial, particularly for nonweight-bearing bones. 2. Sedentary women may increase bone mass slightly by becoming more active but the primary benefit of the increased may be avoiding the further loss of bone that occurs with inactivity. 3. Exercises cannot be recommended as a substitute of hormone replacement therapy at the time of menopause. 4. The optimal program for older women would include activities that improve strength, flexibility, and coordination that may indirectly, but effectively, decrease the incidence of osteoporotic fractures by lessening the likelihood of falling.

Scientific Prerequisites for the Human Exploration of Space

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Critical Research Issues

The lack of scientific data in some areas leads to unacceptably high risks to any program of extended space exploration by humans. These critical research issues concern those areas that have the highest probability of being life threatening or seriously debilitating to astronauts and that are thus potential “show stoppers” for human exploration. The areas in which additional scientific information must be obtained prior to extended exploration of space by humans include the:

6. Detrimental effects of reduced gravity and transitions in gravitational force on all body systems (especially the cardiovascular and pulmonary systems) and on bones, muscles, and mineral metabolism, together with possible countermeasures;

Optimal Performance Issues

The second category of research includes issues that, based on current knowledge, do not appear to pose serious detriments to the health and well being of humans in space. They could, however, result in reduced human performance in flight or on planetary surfaces and, thus, in a less than optimal return from the mission. Some of these issues may become critical research issues relative to long-term human space-flight and return to terrestrial gravity following extended flights, or when extraterrestrial habitation is considered.

BONE DEGENERATION AND MUSCLE ATROPHY

Microgravity has major, potentially dangerous effects on human physiology. Extensive research is required to understand the responses of humans to microgravity and to assess their implications for long-duration space flight. Because a small number of astronauts and cosmonauts have survived long-duration missions in low Earth orbit, there is a false perception that there is no need to be concerned about health-related issues when contemplating interplanetary voyages. According to the Committee on Space Biology and Medicine, "Based on what we know today, this assumption of continued success cannot be rigorously defended. The committee continued, "If this country is committed to a future of humans in space, particularly for long periods of time, it is essential that the vast number of uncertainties about the effects of microgravity on humans and other living organisms be recognized and vigorously addressed. Not to do so would be imprudent at best—quite possibly, irresponsible.”

The bone degradation (osteopenia) and muscle atrophy that occur in a microgravity environment are severe hurdles to an extended human presence in space. The primary risk is to the functioning of the musculoskeletal system upon reexposure to planetary gravity. At present, our understanding of the causes of space-induced osteopenia and muscle atrophy is inadequate to devise effective countermeasures to be taken on long-duration space missions. Also lacking are data on the temporal sequence of bone remodeling and muscle atrophy in prolonged exposure to microgravity and the ways in which these processes may depend on other risk factors such as age, gender, race, or nutrition. Without such data, we cannot be confident that a prolonged microgravity mission such as a Mars flight would not lead to irreparable musculoskeletal damage. Such damage could both impair the effectiveness of crew members during their stay on Mars and pose serious problems upon their return to Earth. There is also

the possibility that some bone demineralization will occur during prolonged flight in spite of countermeasures. If so, astronauts en route to Mars might be at risk for bone fracture with mild trauma and for the formation of kidney stones.

There is great depth and breadth to current research on osteopenia, muscle atrophy, and their underlying causes, thanks to sponsorship by the National Institutes of Health. These studies have concentrated on the problems of bone metabolism in relation to aging, menopause, endocrine disorders, poor nutrition, immobilization, and extended bed rest. A major effort is now needed to develop parallel studies to acquire basic knowledge about these problems as they occur in microgravity and to begin devising appropriate countermeasures. A critical factor in such studies must be the use of appropriate animal models and the development of computational and experimental methodologies to test and validate mechanisms of bone remodeling and muscle conditioning. In addition, the development of suitable in vitro systems using bone and muscle tissue cultures should be undertaken.

One approach to counteracting the physiological effects of microgravity is to subject organisms in space to artificial gravity. Although such an environment could correct bone degeneration, muscle atrophy, and other changes due to microgravity, it could also exacerbate other effects not now perceived to be major problems. Head movements made in a spinning environment or Coriolis effects can lead to disturbing vestibular sensations and motion sickness. Changes in gravity experienced when moving to different parts of a spinning spacecraft or when changing the spin rate might induce symptoms of disequilibrium.

A comprehensive program is required to (1) determine the gravity threshold required to reverse or prevent the deleterious effects of microgravity and (2) evaluate the effects of centrifugation on behavior and/or sensorimotor function. Part of the required research could be accomplished by using human surrogates, including nonhuman primates, on a dedicated centrifuge in low Earth orbit. Studies of human responses to spinning will require a centrifuge of sufficient dimension to accommodate humans. An alternative strategy would be to investigate the use of rotating tethered spacecraft to provide artificial gravity. It is possible that the detrimental vestibular effects of spinning can be eliminated if the tethers are sufficiently long.

Even assuming an optimistic schedule for lunar operations or space station activation, the relevant life-sciences knowledge developed from them will probably not be available before the beginning of the second decade of the 21st century. This implies a substantial technical risk in any program of Mars exploration that relies on a comprehensive solution to problems of human adaptation to microgravity. The prudent alternative is to carry forward, during conceptual design phases, alternatives providing for artificial gravity (as recommended in a National Research Council report) during the cruise flight phase, and possibly in Mars orbit as well. If satisfactory countermeasures are confidently identified during a vigorous and rigorous program of orbital life-sciences research, this alternative design path can be abandoned. Conversely, if an effective artificial-gravity system is developed, research on countermeasures will become less urgent.

The design, construction, and operation of rotating spacecraft may pose formidable technical challenges. Nonetheless, all investments in the program will otherwise be hostage to a favorable outcome in the human adaptation issue. In the view of CHEX, the Synthesis Group's report erred ab initio in discarding consideration of artificial-gravity scenarios in its four architectures. Indeed, the provision of artificial gravity may well prove to be an architectural variable of more fundamental importance than the thematic differences between alternative mission emphases presented in the report of the Synthesis Group.

Conclusions

The Committee on Human Exploration finds that a program for the exploration of the Moon and Mars by humans offers both challenges and opportunities for the participation of the scientific community. Foremost is the fact that particular, enabling scientific information is required if a Moon/Mars program is ever to succeed in one of its prime goals, the expansion of human presence and human activity beyond Earth orbit into the solar system. This will remain the case even if a major Moon/Mars program is not initiated for 5 years or 25 years. The information that the committee deems critical is concerned largely with aspects of space biology and medicine and associated characteristics of the radiation environment. This in itself is not a new finding; recognition of the need for such information has been building over the past 30 years with little progress on solutions. What is required is that NASA (and other agencies involved in implementing a human exploration project) make a long-term commitment to sponsoring a rigorous, efficient, high-quality research program on the ground and in space. The resources required will be significant and challenge NASA to structure, market, implement, and ultimately manage an adequate plan.

To enable long-duration human flight to, and operations on, the Moon and Mars, we must obtain critical relevant data. However, we must also consider ab initio that the enabling research has a purpose above and beyond the simplistic, but prime, goal of achieving human presence and implied elementary survival. If a Moon/Mars program is to accomplish more than merely establishing a human presence in space, then achieving the program's yet-to-be-established specific goals and objectives demands that human performance and "pre-presence" preparation be optimized. This imperative places additional weight on the acquisition of scientific data on, for example, the distribution of potential lunar resources, details of the atmosphere of Mars, and information on the physical, chemical, and biological properties of the Martian surface.

Science permeates all aspects of human exploration, no matter which architecture is finally selected and regardless of which set of candidate goals and objectives evolves. The involvement of the scientific community is needed to help set the goals for purely robotic missions, to analyze both scientific and engineering data, to structure appropriate tasks for humans, and to assist in the optimal integration of human and robotic activities. This pervasive requirement for scientific input mandates that the piloted spaceflight community develop a new understanding of and attention to the conduct of space science. It simultaneously requires that the scientific community interact constructively with those charged with implementation of a Moon/Mars program. In fact, success will require a technical and programmatic approach that eliminates the historical dichotomy between the "manned" and "unmanned" spaceflight programs.

MUSCULOSKELETAL DISCIPLINE SCIENCE PLAN, 1991

Space Physiology and Countermeasures Program

Life Sciences Division, NASA, Washington, DC.

Flight research, which also uses both human and animal subjects, primarily addresses the questions of "What happens to the musculoskeletal system during weightlessness?" and "What effects do certain countermeasures have?" These flight data have been obtained from subjects on both U.S. and U.S.S.R. missions. Countermeasures that have been examined on the ground and/or in flight include various types and prescriptions of exercise, electrical stimulation, pharmacology, changes in nutrition, and muscle stretch. Artificial gravity is a potential countermeasure for musculoskeletal effects of space flight.

1.3 GOALS AND OBJECTIVES

1.3.1 Goals

The overall goals of the NASA Musculoskeletal Discipline Research Program are to:

- Ensure adequate physiological and performance countermeasures

The achievement of these goals is predicated on specific objectives concerned with understanding the mechanisms whereby the organism, tissue, cells, organelles, and extracellular matrix of muscle, bone, and connective tissue

- achieve and maintain Earthbound homeostasis
- function in either a microgravity environment or under conditions of non-weightbearing
- undergo adaptive changes in structure and function in response to prolonged exposure to a microgravity environment
- respond to a variety of countermeasures (mechanical, hormonal, pharmacologic) designed to maintain normal structure and function in the face of prolonged exposure to a microgravity environment as undergo readaptation to Earth's gravity.

1.3.2 Objectives

The specific objectives leading to the attainment of the goals of the research program are to:

- Develop and verify ground-based human and animal models to study musculoskeletal changes.

This plan incorporates recommendations from reports by the Committee on Space Biology and Medicine (Goldberg), the NASA Life Sciences Strategic Planning Study Committee (Robbins), and the Federation of American Societies for Experimental Biology (FASEB) (see List of References).

Current knowledge about physiological changes associated with short-term and long term space flight is summarized in Appendix 1, which is from Space Physiology and Medicine, 2nd edition, by Drs. Nicogossian, Leach Huntoon, and Pool.

Final Report Phase III: Research Opportunities in Bone Demineralization

NASA Contractor Report 3795, April 1984

SUMMARY

Bone demineralization and negative calcium balance have been reported consistently as a physiological response to space flight. Additionally, changes in calcium metabolism have been observed that may be associated with bone loss and a possible increased risk of fracture. The changes include increased fecal loss of calcium and hypercalciuria with a possible change in potential for formation of calcium-containing renal stones. In United States space flights as long as 3 months and Soviet flights as long as 7 months, neither loss of bone mineral nor the resultant hypercalciuria has been associated with impaired functional capacities of astronauts. However, concern for the health, effectiveness, and safety of space crews during and following extended or repeated space flights requires that gaps in knowledge of bone demineralization be identified and priorities for future research efforts be indicated.

The processes underlying bone loss in man during space flight are poorly understood. Histomorphometric studies of bone changes in rats flown aboard Cosmos biosatellites suggest that periosteal bone formation is inhibited and endosteal bone resorption is unchanged in weight-bearing bones in this species. Information concerning bone loss in weightlessness has also been obtained in ground-based studies of suspended rats, immobilized monkeys, and normal human volunteers during bed rest. Comparison of histomorphometric changes in bone of rats during space flight with bone changes in the suspended rat model and with bone changes in a monkey model indicates that some changes are similar for these models despite differences in bone growth and remodeling systems of the two species. Histomorphometric studies of bone changes in man have not been done during space flight or uncomplicated bed rest.

Evidence for loss of bone mineral in man during space flight has been supplied by metabolic balance studies and by non invasive measures of bone density changes. These studies indicate an overall difference between anabolic and catabolic processes but provide little information concerning the changes occurring in bone during weightlessness. Metabolic balance studies in man during bed rest have shown changes in calcium balance generally similar to those of astronauts during space flight. Increased urinary and fecal losses of calcium have been reported in each situation. It has not been determined whether the fecal losses represent increased endogenous losses or decreased intestinal absorption of calcium. Noninvasive measures of bone density indicate that preferential loss of calcium from weight-bearing bone (os calcis) is common to space flight and bed rest.

Studies of changes in levels of calcitropic hormones (parathyroid hormone, vitamin D, and calcitonin) during space flight and bed rest do not consistently indicate changes of a magnitude that would ordinarily be associated with increased mobilization of bone. It is difficult to draw conclusions from these data, because at the time the measurements were made in space flight and in published reports of bed-rest studies, assays for a number of hormones were not well refined. Plasma levels and urinary excretion of cortisol are increased in man during space flight and adrenal glands are enlarged in rats following flights of the Cosmos biosatellites. However, urinary excretion of cortisol is not increased during bed rest. General systemic effects of endocrine agents cannot readily explain the local and preferential demineralization of weight-bearing bones. However, since physiologic responses during weightlessness differ from those under gravity, it may be possible that responses of bone cells to normal levels of endocrine agents in weightlessness differ from responses on the ground. This may be particularly evident in weight-bearing bones that lack their normal gravity-related stimuli.

Trials of countermeasures to prevent bone demineralization have been conducted in crews during space flight and, more extensively, in ground-based studies of human subjects during bed rest. Exercise during space flight has not completely reversed negative calcium balance or hypercalciuria. However,

there is some evidence that use of a treadmill during space flight may have moderated loss of os calcis mineral. In Soviet flights exercise has reportedly been associated with decreased calcium loss. A number of levels of weight-bearing and/or exercise regimens have been tested in ground-based bed-rest studies in the United States in an effort to determine the amount of physical stress necessary to prevent calcium loss. Of all the protocols evaluated, only controlled ambulation on a prescribed course for 4 hours completely alleviated negative calcium balance. Dietary intervention (supplementation of fluoride or supplementation of calcium and phosphorus) did not reverse hypercalciuria or negative calcium balance over a long period of bed rest. A combination of calcium and phosphorus supplements, longitudinal compression and administration of synthetic salmon calcitonin was partially effective for a shorter period; however, administration of synthetic salmon calcitonin or longitudinal compression alone was not effective. Diphosphonates (EHDP or clodronate) administered to normal subjects during bed rest have been the most effective pharmacologic agents tested. However, side effects of these particular compounds contraindicate their further use.

The following report comprises an overview of bone demineralization during space flight, observations of the ad hoc Working Group on the NASA Biomedical Research Program in Bone Demineralization and experiments related to bone loss planned for Spacelab flights, and suggestions for further research. The observations of the ad hoc Working Group focused upon the following topics: (1) pathogenesis of bone demineralization, (2) potential for occurrence of renal stones consequent to prolonged hypercalciuria, (3) development of appropriate ground-based and in-flight models to study bone demineralization, (4) integration of research efforts, and (5) development of effective countermeasures. Priorities for further research are indicated.

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APPENDIX D

CARDIOVASCULAR DISCIPLINE - SUPPORTING MATERIAL

D-1 - Cardiovascular Discipline Report of Countermeasures

Impact of Spaceflight on Cardiovascular Operational Functions

Reduced Orthostatic Function. Predisposition to hypotension and syncopal symptoms during standing, head-up tilt, or lower body negative pressure (LBNP) is well-documented in astronauts following spaceflight [6,8,12,15,23,57,61,74,83,95]. Orthostatic hypotension has been associated with numerous alterations in cardiovascular function (see below). An important operational concern is the postflight presence of orthostatic intolerance with frank syncope in 30-40% of Shuttle crews when not protected by a G-suit and fluid loading [8,9] and 6-9% who are unable to affect immediate egress from the vehicle [77].

Physical deconditioning associated with exposure to microgravity may contribute to reduced effectiveness of blood pressure control during orthostatic challenges following spaceflight because exposure to groundbased simulations can induce higher incidence of syncope in exercise-conditioned subjects compared to their sedentary counterparts [23,81]. This observation provides a basis for the contention that cardiovascular adaptation associated with physical stress may prove to be effective in protecting underlying mechanisms of postflight orthostatic hypotension.

Reduced Physical Work Performance. In the absence of countermeasures, post-flight maximal oxygen uptake (Vo_{2max}) can be decreased by approximately 20% following only 9 to 14 days [68]. Reduced stroke volume and cardiac output are the primary factors contributing to lower aerobic capacity [58,68,81]. In addition to reduced cardiac output, there are also reductions in skeletal muscle blood flow [40] and aerobic pathway enzymes [37,56] which could contribute to limit oxygen delivery and utilization. Vo_{2max} actually increased over the course of the spaceflight in the Skylab 4 crew [15,71]. This was associated with an intensive daily inflight exercise program and indicated that a training effect took place. The commander of Skylab 4, who undertook the least extensive exercise training program both before and during flight compared to other two crewmembers, showed the smallest decrement in Vo_{2max} . This may indicate that intensive exercise may not always be necessary for all individuals during spaceflight. Identification of the minimal amount of exercise needed to maintain pre-flight fitness levels has received little attention to date or whether it is indeed necessary to maintain pre-flight fitness throughout long flights.

Changes in Cardiac Structure and Function

In the absence of some intrinsic disease state, the primary determinants of cardiac structure, mechanical and electrical function and vascular performance include: a) autonomic nervous system function; b) extrinsic cardiac and vascular mechanical loading; c) nutrition and d) drugs and other toxins. There are few data that define if and how these factors may be altered during long duration space missions, with the potential of compromising cardiac structure and function.

Current data suggest that highly trained, well-conditioned healthy young and middle-aged individuals who undertake a relatively active life style in microgravity, with at least moderate exercise, can survive and perform useful work for at least 180 days (and perhaps at least 270 days) with no major overt health problems. At the end of this period, such individuals can return to earth and, though they may require weeks to readapt and function normally, they appear to recover without sequelae manifest within 5-10 years. Remaining unknowns include: a) capacity of such people to function adequately in emergency

setting upon reentry; b) capacity to function in microgravity, and upon reentry, during microgravity exposures longer than 6 months; c) deleterious effects of microgravity exposure which become apparent more than 10 years after reentry; and d) impact of microgravity environment on individuals who are older, less well conditioned or who differ in other important ways from the well circumscribed population thus far exposed to microgravity.

Data which have already been analyzed (a small fraction of the total available database) suggest that no major irreversible cardiovascular changes, involving either the heart itself or the vasculature, occur in response to microgravity exposure as defined above. Although few data are available specifically defining the response to microgravity of cardiac structure and performance or intrinsic myocardial function, echocardiographic data provide evidence that cardiac chamber size is reduced in microgravity [3,10,73]. New data using MRI technology provides evidence that this change may represent cardiac muscle atrophy (Blomqvist, unpublished data). This cardiac mass reduction could result from reduced vascular volume and/or interstitial space fluid in the heart. However, dramatic reductions in baseline [10,21,42], orthostatic [6,21,42] and exercise [3,15,68] stroke volumes appear to be primarily the result of lower blood volume since indices of ventricular function (e.g., ejection fraction, aortic pulse wave velocity) are not altered or may actually increase [3,15, 23,73].

Groundbased experiments have demonstrated increases in β_1 -adrenergic responsiveness following 16 days of head-down tilt [22]. A given adrenergic discharge would be expected to lead to excessive tachycardia with such alterations, a well-documented phenomenon associated with postflight standing. Therefore, increased responsiveness of cardiac β_1 -adrenergic receptors represents a mechanism that may contribute to orthostatically-induced tachycardia following exposure to low gravity.

Small data sets of rhythm recordings suggest the likelihood of ventricular dysrhythmic activity may be related to the duration of microgravity exposure. Arrhythmias observed have included non-sustained ventricular tachycardia. Similar data sets indicate that, during exposure to microgravity, both heart rate and blood pressure are lower than on earth. Although the incidence of cardiac dysrhythmias has not increased during space missions of duration less than 10 days [48], they have been reported during both spaceflight and groundbased analogues of microgravity with exposures of longer than two weeks. Pre-ventricular atrial contractions (PACs), supraventricular and ventricular contractions, and nodal bigeminy were reported in Apollo 15 crew members who had not experienced such dysrhythmias before flight [54]. During provocative adrenergic agonist testing, increased occurrence of junctional or nodal arrhythmias was observed following head-down bedrest [22]. This is particularly intriguing in light of observations that altered autonomic function was postulated as a possible mechanism underlying changes in junctional rhythm frequently observed in astronauts during the U.S. Skylab missions [86]. There were no junctional rhythms in 8 subjects during adrenergic agonist infusion tests conducted before head-down bedrest. However, following 14 days of exposure to low gravity, isoproterenol induced junctional rhythms in three subjects, with pre-ventricular contractions (PVC's) occurring in one those subjects and pre-atrial contractions (PAC's) occurring in another. Phenylephrine infusion was associated with junctional rhythm for 2 minutes with 1 interpolated beat in one subject, junctional rhythm and PVCs in one subject, bradycardia of 35 bpm with erratic rhythm with escape beats in one subject, and PACs in one subject. These observations indicate that exposure and adaptation to microgravity may increase risk of cardiac arrhythmias.

Structural and Functional Changes of the Vasculature

Changes in Venous Vasculature. There is compelling evidence based on occlusion plethysmography of the legs that venous compliance of the legs (calf) is increased by exposure to microgravity [14,91]. Reduction of leg muscle size in humans with the use of a low gravity model (head-down tilt) increased venous compliance, supporting a causal relationship that a loss in the muscle compartment surrounding the large veins will increase their compliance. Muscle mass causes mechanical compression on the veins that can act to resist venous stretching and consequently reduce blood volume accumulation under a given change in hydrostatic pressure. Leg compliance appears to be less when there is a large muscle mass providing mechanical resistance to limit expansion of the veins. Therefore, an increase in venous compliance in low gravity seems reasonable since a loss of muscle mass in the legs due to disuse in microgravity and bedrest is well established [37,56,91]. Attenuation of autonomically activated vascular smooth muscle, baseline contractile activity or skeletal muscle and venosomatic reflexes [90], and factors other than muscle structure, such as vascular wall structure and fluid shifts from the legs to the circulation, can also contribute to the overall state of venous compliance. Although not yet demonstrated, the possibility that low gravity may induce physiologically significant alterations in one or more of these other determinants of limb compliance cannot be ruled out. However, relationships derived from previous investigations [13,14] suggest that muscle size alone is the primary contributor to elevated limb compliance in subjects exposed to low gravity. Although increased venous compliance would enhance blood pooling in the lower extremities during orthostasis, there is little evidence that pooling of fluid in the legs is increased following actual or simulated microgravity [6,42].

Changes in Arterial Vasculature. Numerous investigators have reported that exposure to low gravity reduced baseline blood flow [5,21,28,49] and maximal conductance [40] in the vasculature of the arms and legs, suggesting that spaceflight may alter arterial structure and function. Reduction in maximal conductance was associated with greater muscle fatigability [40]. Excessive sympathetic discharge following exposure to actual or simulated microgravity, as evidenced by large elevations in plasma catecholamines during standing [94,98] and increases in urinary noradrenaline and its metabolites [64,67], probably represent the primary mechanism of vasoconstriction and reduced blood flow. Increased vasoconstrictive state appears to be coupled to lower plasma volume since replacement of vascular volume lowers forearm vascular resistance following exposure to head-down tilt [94].

Autonomic and Baroreflex Regulatory Function

Altered Autonomic Balance. Power spectral and time series analyses of baseline R-R intervals from subjects exposed to groundbased analogues of microgravity indicate reductions in high frequency (0.25 Hz) spectrum and standard deviations of R-R intervals, suggesting a reduction in parasympathetic activity [30]. Reduction in diurnal variabilities of heart rate and systolic and diastolic pressures [48] in astronauts during spaceflight supports the notion that parasympathetic activity is reduced.

Although direct measurements of sympathetic nerve activity have not been conducted on individuals exposed to low gravity, reduction in plasma catecholamines during groundbased analogues [21,22,50] and spaceflight [65,80] support the hypothesis that reduced sympathetic stimulation and discharge might be expected with exposure to low gravity environments. However, excessive sympathetic discharge following exposure to actual or simulated microgravity is evidenced by large elevations in plasma catecholamines during standing [94,98] and exercise [41] with concomitant cardioacceleration. Such increases would be expected under conditions of hypovolemia and orthostatic hypotension.

Enhanced Aortic-Cardiac Baroreflex Responsiveness. Although the ability to investigate aortic-cardiac baroreflex function in humans is limited by the anatomical location of baroreceptors, the isolation of aortic baroreceptors has been attempted with the application of neck chambers and lower body negative pressure devices designed to 'clamp' carotid and cardiopulmonary baroreceptor activity during selective pharmacological stimulation [27,29]. When these procedures are applied, it is clear that the heart rate response to aortic baroreceptor stimulation is enhanced following exposure to low gravity [29]. Although this enhanced baroreflex responsiveness may reflect alteration in autonomic function, it appears that a primary underlying mechanism is the hypovolemia associated with low gravity exposure since normovolemia reverses the heightened response [27]. Thus, restoration of plasma volume should alleviate the primary change in aortic-cardiac baroreflex response.

Impaired Carotid-Cardiac Baroreflex Function. Despite greater standing tachycardia after spaceflight, standing heart rates were lower in syncopal compared to non-syncopal subjects following head-down tilt [16] and began to decline as the duration of spaceflight became longer than 10 to 12 days [74]. These observations raised the possibility that low gravity causes impairment of cardioacceleratory reflexes elicited by carotid baroreceptors since aortic baroreceptor stimulation was associated with enhanced chronotropic response (see above). Impairment of this vagally-mediated carotid-cardiac baroreflex has subsequently been demonstrated after groundbased analogs [16,36] and actual spaceflight [46,74] and its magnitude of attenuation correlated positively with development of orthostatic hypotension and instability (syncope) immediately upon standing [16].

A prominent feature of the change in carotid-cardiac baroreflex adaptation to low gravity is a shift of the stimulus-response relationship downward and to the right, producing a lower gain (less maximum response slope). This indicates that for a given reduction in arterial pressure, there will be a smaller compensatory increase in heart rate after adaptation to low gravity. Since there is little change in baseline mean arterial pressure, elevation in baseline heart rate places the operational point at a lower position near the threshold on the response curve. This relocation of operational point on a less responsive part of the stimulus-response relationship (near threshold in the hypotension range) further compromises the capacity of this reflex to increase heart rate in the face of an orthostatic challenge such as simple standing. Acute alterations in plasma volume do not affect carotid-cardiac baroreflex response [89] and the time course of changes in baroreflex function during bedrest do not parallel that of plasma volume [16]. These data suggest that, unlike aortic-cardiac baroreflex function, impaired carotid-cardiac baroreflex function occurs during low gravity independent of plasma volume reduction and probably cannot be countered with treatments that address the mechanism(s) that control fluid homeostasis.

These alterations in carotid-cardiac baroreflex provide mechanisms that can explain several clinical observations regarding the development of orthostatic hypotension and intolerance following long-term exposure to low gravity. The increase in standing heart rate following spaceflight can be explained by hypovolemia that elicits an exaggerated cardiac response from aortic baroreceptor stimulation. However, some individuals with pronounced orthostatic hypotension after extended exposure to head-down tilt demonstrated less tachycardia during standing than subjects who maintained blood pressure [165], and orthostatic instability after spaceflight was associated with a lower operational setpoint [47]. The observation that reduced maximum gain and lower operational point of the carotid-cardiac baroreflex stimulus-response relationship were associated with orthostatic intolerance [16,47,69] supports the notion that impairment of this reflex function may represent a major autonomic disorder associated with low gravity.

Reduced Vasoconstrictive Reserve. Numerous investigators have reported that exposure to low gravity increased baseline peripheral vascular resistance [21,30,49]. Reflex peripheral vasoconstriction induced by activation of cardiopulmonary baroreceptors in response to a reduction in central venous pressure (CVP) is a basic mechanism for elevating systemic vascular resistance and defending arterial blood pressure during an orthostatic challenge. When hypovolemia is induced in ambulatory subjects, forearm vascular resistance (FVR) is elevated with an upward shift of the stimulus-response curve compared to a normovolemic baseline state [89]. Since the vascular system has a finite vasoconstrictive capacity, it is reasonable to interpret elevated FVR during hypovolemia as representing a reduction in the reserve capacity for further vasoconstriction. The increased slope, or gain, of the cardiopulmonary baroreflex response induced by hypovolemia demonstrates a more responsive peripheral vasoconstriction in a volume-depleted state compared with normovolemia. This appears to be an appropriate adjustment to defend arterial blood pressure. However, the increased cardiopulmonary baroreflex gain represents utilization of vasoconstrictive reserve which, depending on the degree of hypovolemia, could significantly compromise the capacity to provide adequate vascular resistance during orthostatism. Since hypovolemia occurs in low gravity, inadequate elevation of peripheral vascular resistance and maintenance of arterial pressure during standing immediately after exposure to groundbased analogues or actual spaceflight can limit orthostatic function.

Reduction in Central Venous Pressure. Recent spaceflight data indicate that central venous pressure (CVP) is reduced immediately upon entry into orbit [7]. Although the mechanism(s) is unclear, increased cardiac compliance has been proposed with the observation that stroke volume is maintained despite reduced filling pressure [96]. Beyond the acute phase of spaceflight, there is a chronic reduction CVP associated with low gravity [20,61] that may represent an alteration in autonomic functions associated with feedback regulation of blood volume [26]. There is compelling evidence that the reduction in CVP observed during long duration exposure to low gravity represents a 'resetting' of CVP to a lower operating point. Evidence to support this hypothesis includes failure of fluid input to effectively expand plasma volume [94], similar volumes of fluid infusion induce similar volumes of urine excretion despite lower plasma volume in low gravity compared to normal gravity [33], and exposure to head-down tilt caused the cardiopulmonary baroreflex stimulus-response relationship to shift to the left so that the response for peripheral vascular resistance occurred in a lower range of CVPs [21,26]. Physiologically, these observations suggest that low gravity causes a resetting of volume control mechanism(s) to a lower operational range for CVP. Clinically, this adaptation will limit the capacity for replacement of plasma volume by simple drinking techniques.

Autonomic resetting of low-pressure baroreceptors to a lower operating range of CVP has two potentially compromising consequences. First, there is less vasoconstriction at the same level of hypovolemia and CVP following exposure to low gravity compared to that of ambulatory hypovolemia. Therefore, less vascular resistance can be developed in the face of low plasma volume and blood pressure after exposure to low gravity. Second, lower CVP during orthostatic challenge during low gravity is associated with lower cardiac filling and stroke volume, factors that will also limit appropriate blood pressure regulation. Therefore, the adaptation of the cardiopulmonary baroreflex to low gravity can compromise the capacity to increase both cardiac output and peripheral vascular resistance, the two factors that dictate maintenance of arterial pressure during standing.

Finally, the integration of various baroreflex systems should be appreciated. There is evidence that cardiopulmonary baroreceptor unloading results in elevated sensitivity of aortic baroreceptors [4]. Since low gravity reduces blood volume and CVP, reduced tonic inhibition of aortic baroreceptors associated

with cardiopulmonary baroreceptor unloading may represent a primary mechanism that contributes to the accentuation of aortic-cardiac baroreflex gain observed with low gravity.

Adrenoreceptor Hypersensitivity. It has been postulated that orthostatic hypotension associated with exposure to low gravity may be partly attributable to adrenergic receptor hypersensitivity in the face of excessively high sympathetic activation [80].

β_2 adrenergic responsiveness was increased in subjects exposed to 16 days of a groundbase analogue of microgravity without affecting α_1 -vascular responses [22]. Because vascular β_2 -adrenoreceptors elicit vasodilation compared to vascular constriction mediated by α_1 -adrenoreceptors, the overall effect of greater β_2 responsiveness in the absence of changes in α_1 responses could produce a lesser vasoconstrictive effect, especially under a condition of increased sympathetic discharge during standing after exposure to low gravity. This hypothesis is supported by the observations that maximal contractile tension in isolated rat aorta evoked by norepinephrine, phenylephrine and vasopressin was diminished by 14 days of head-down tilt [32] and that normal reductions in blood flow to inactive muscle and visceral tissue during exercise did not occur in rats exposed to head-down tilt [70]. The potential to limit orthostatically-induced elevations in peripheral resistance could compromise the capacity of the cardiovascular system to maintain adequate arterial blood pressure and cerebral perfusion during standing. This is consistent with the observation that astronauts who could not complete a 10-min stand test following spaceflight as a result of severe presyncopal symptoms had significantly less elevation in their peripheral resistance compared to that of astronauts who successfully completed the stand test [6].

Especially in the setting of hypovolemia, excessive adrenergic discharge observed upon standing after exposure to low gravity might be ineffective in maintaining upright blood pressure, and baroreceptor-mediated elevations in heart rate might be further enhanced. Since excess tachycardia and contraction against a nearly empty ventricular chamber is known to trigger the Bezold-Jarisch response [85], increased cardiac β -adrenoreceptor hypersensitivity may be an underlying mechanism for orthostatic hypotension and vasovagal syncope associated with low gravity. Although speculative, this possibility has practical implication for development of possible treatments. For example, the use of a β -blocker prior to reambulation might reduce the potential for a vasovagal event. Also, regular exercise has been associated with reduced β -adrenoreceptor hypersensitivity [11]. Combined with treatment to diminish volume losses, exercise and pharmacological countermeasures might improve orthostatic stability at critical times following reentry.

Role of Skeletal Muscle in Neural Control of Blood Pressure. Neural activity which is responsible for recruitment of motor units in the cerebral cortex and stimulation of mechanoreceptors and metaboreceptors in the contracting muscle reflexively activate cardiovascular control areas in the ventrolateral medulla [35,72]. These central command mechanisms therefore link skeletal muscle activity to autonomic efferent control of the heart and blood vessels. Since there is significant atrophy of skeletal muscle [37] and reduction in skeletal muscle blood flow (see above) during spaceflight, it is possible that the interaction between muscle afferent neural input and central command may be altered. Likewise, it is possible that specific exercise countermeasures may be designed that can enhance the gain between muscle afferent neural input and central command so with muscle movement during standing following spaceflight, there is increased MSNA to the heart and blood vessels, acting to elevated cardiac output and vascular resistance to defend against development of orthostatic hypotension.

Changes in Vascular Volume

As much as 20% reductions in plasma and blood volume are induced by spaceflight [1,2,26], occurring in the initial 24 h of the mission followed by a new equilibrium at a lower volume which is maintained for the remainder of the flight [1,2,26]. Reduction in total circulating blood volume is related to greater tachycardia during standing after spaceflight [9,16,57], suggesting that vascular volume can be an important contributing factor to post-spaceflight orthostatic hypotension and instability. Although the mechanisms are unclear, normal urine output and renal function in the presence of normal fluid intake throughout exposure to low gravity suggest that plasma volume reduction and failure for its maintenance at 1G levels during low gravity is not associated with clinical renal dysfunction [25,26]. A rapid diuresis occurs within the initial 24-48 h of exposure to groundbased analogs of microgravity [26], with a magnitude that can account for the amount of plasma volume reduction. The diuresis may be partly explained by stimulation of mechanoreceptors that leads to a release of atrial natriuretic peptide [51] and a fall in ADH, renin and aldosterone [31].

Compelling evidence suggests that prolonged reduction in CVP during exposure to microgravity reflects a 'resetting' to a lower operating point which acts to limit plasma volume expansion (restoration) during attempts to increase fluid intake [26,33]. In groundbase and spaceflight experiments, successful restoration and maintenance of plasma volume prior to returning to an upright posture may depend upon development of treatments that can return CVP to its baseline 1G operating point. Fluid-loading and LBNP have not proved completely effective in restoring plasma volume, suggesting that they may not provide the stimulus to elevate the CVP operating point. On the other hand, exercise, which can chronically increase CVP [18,84], has been effective in expanding plasma volume when combined with adequate dietary intake of fluid and electrolytes [26]. Therefore, there is adequate justification for the use of exercise in restoring or maintaining plasma volume following adaptation to spaceflight.

Because reduction of blood volume during spaceflight is related to orthostatic instability, it seems reasonable that exercise regimens designed to promote hypervolemia might prove effective against orthostatic hypotension. However, data from both spaceflight and ground experiments do not necessarily support this hypothesis. Despite extensive exercise training which increased $\text{Vo}_{2\text{max}}$ by 8%, the three astronauts who completed the 84-day Skylab 4 mission experienced 16% plasma volume reduction, increased venous compliance, and orthostatic instability postflight [15]. Conversely, in a groundbase experiment [52] with intensive cycle exercise training performed for two 30-min periods per day for five days per week during HDT, $\text{Vo}_{2\text{max}}$ and plasma volume were maintained at pre-HDT levels, while groups who performed resistance or no exercise experienced significant reductions in these parameters. However, tolerance time during head-up tilt were significantly reduced in all three groups with no difference between them. Because blood volume was maintained in the cycle-trained subjects, physiological mechanisms in addition to hypovolemia must contribute to orthostatic intolerance. These results from spaceflight and ground studies suggest that repeated exercise training regimens, designed to defend physical fitness, require more specificity to provide appropriate stimuli to the mechanism(s) that control orthostatic stability.

Alterations in autonomic function during exposure to low gravity may have direct effects on blood volume regulation. It has been postulated that lower sympathetic stimulation and discharge in low gravity may contribute to hypovolemia and anemia that accompany spaceflight [80]. Renal denervation substantially increases renal sodium loss. Patients with the Bradbury-Eggleston syndrome, who suffer from the degeneration of peripheral autonomic nerves, particularly illustrate this natriuretic effect while kidney production of dopamine is relatively normal [79]. The expected effects of this neurohumoral alteration would fit the observed reduction in circulating plasma volume and sodium observed in

spaceflight and at bedrest that is accompanied by a reduction in plasma renin activity [31]. Therefore, it is possible that a reduction in sympathetic activation and circulating norepinephrine in low gravity could result in increased renal sodium loss because the natriuretic effect of dopamine would be unopposed. This could contribute to the reduction in plasma volume that occurs in the course of the first day of spaceflight. While the central fluid shift seen with low gravity may have the most consequential effect on reduced plasma volume, the specific role of renal sympathetic activity deserves further investigation.

In addition to a loss in plasma volume, the hypovolemia induced by prolonged exposure to low gravity can be contributed to by a more gradual reduction in red cell mass [34,60,66], probably due to a fall in erythropoietin levels [1,2,66]. An association between the sympathetic nervous system and erythropoiesis has been supported by the observation that the reticulocyte response to acute bloodletting was greatly diminished after renal denervation [87]. Intravenous administration of the b-adrenergic receptor agonist salbutamol increased serum erythropoietin [43] while b-blockers blunted the erythropoietin response to hypoxia [44]. These experimental results provide compelling evidence that sympathetic stimulation, acting through b2-adrenoreceptors, may modulated erythropoiesis through increased erythropoietin production. Thus, reduced sympathetic activity and reduced circulating norepinephrine associated with low gravity could represent an underlying mechanism for the anemia observed with space travel and bedrest.

Following space missions of less than 7 days duration, ingestion of approximately one liter of isotonic saline reduced the heart rate response and maintained blood pressure in astronauts during post-spaceflight stand tests. This observation supported the hypothesis that body fluid loss was a primary mechanism of orthostatic compromise following spaceflight [10,97]. However, when stand test experiments were conducted on bedrested subjects or astronauts who had been exposed to low gravity for durations at or beyond one week, it became apparent that hypovolemia alone could not explain orthostatic compromise since heart rate and blood pressure responses during standing were similar in individuals who did and did not undergo fluid loading procedures [94,97]. It has become apparent that alterations in autonomic functions associated with blood volume and pressure regulation are induced by exposure to low gravity.

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APPENDIX E

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A

E - 2 NEUROLOGICAL COUNTERMEASURES SUMMARY CHARTS

B TRIED AND ACCEPTED COUNTERMEASURES

EARLY SHUTTLE PHASE

CM # 1. PROMETHAZINE INJECTION.

Rationale:	Promethazine has had proven efficacy in ground-based nausea and vomiting due to illness, drug toxicity and motion. ¹
Supporting Research:	Shuttle trials have shown efficacy but no double-blind, placebo controlled trials have been performed. Crew member acceptance is high.
Risk/Benefit Ratio:	Appears to dramatically reduce the impact of SMS on early flight days but a small concern regarding performance remains.
Efficacy:	Although results show improvement in SMS symptoms in 90% of those treated, the improvement varies from major to minor.
Cost-effectiveness:	Inexpensive medication.
Operational ease of use:	Requires crew training for non-physician crew medical officers. Time loss on orbit is minimal. Requires preflight drug testing.
Interference with other countermeasures:	May cause drowsiness at therapeutic doses. More serious side effects mitigated by preflight drug testing. Performance decrements have been noted in ground-based trials; however, drugs such as dexedrine have reduced side effects. Performance decrements on orbit have been minimal since drug is used to treat crew members who are already ill and the pre sleep period is used for treatment when possible.

Recommendations:

(1) Continue using promethazine for SMS symptoms early in mission. (2) Consider small trials of newer medications in the KC-135 for possible future use. (3) Develop an alternative delivery system for dexedrine acceptable for space flight (intranasal, sublingual, patch, injectable, etc.) in case of emergencies which require peak performance after promethazine use. (4) As part of debriefings and review of medical records, more complete information should be gathered on the side effects of promethazine.

¹Jennings, R.T., "Managing Space Sickness," presented at the NASA/NIH Workshop on Vestibular-Autonomic Regulation, Pittsburgh, PA, April 23-24, 1996.

C TRIED AND ACCEPTED COUNTERMEASURES

EARLY SHUTTLE PHASE

CM # 2. CREW TRAINING / BRIEFINGS. *Examples include “limit head movements, maintain 1-G attitude early in flight, maintain cool cabin temperature, use LCG cooling, limit food intake unless hungry, low fat - high carbohydrate diet, maintain hydration, avoid odors, contain vomitus, limit activities that are provocative”.*

Rationale:	Previous crew experiences concerning factors which seem to initiate or exacerbate SMS should be included in crew training.
Supporting Research:	Minimal
Risk/Benefit Ratio:	Essentially no risk
Efficacy:	Variable
Cost-effectiveness:	No cost
Operational ease of use:	It is not always possible to maintain cool cabin temperature. Doffing of the ACES causes head movements. Certain activities following “Go” for orbit ops require stowage of items and movement. Spacelab activation requires movement. Payload operations require movements.
Interference with other countermeasures:	None

Recommendations:

Continue present activities with crew training and briefings.

D TRIED AND ACCEPTED COUNTERMEASURES

EARLY SHUTTLE PHASE

CM # 3. TIMELINE ADJUSTMENTS. *Examples include: “establish minimal duration of flight past SMS period, EVA on Flight Day 3 or later, EVA on Flight Day 2 only in contingencies after crew status check, no EVA on Flight Day 1, crew cross-training, reduced load on crew scheduling on Flight Days 1 and 2.*

Rationale:	Minimize crew work load during the time frame in which SMS is a problem. Timeline adjustments have helped to prevent early mission impact from vestibular disturbances, but impact operations during the first two days of flight.
Supporting Research:	Minimal
Risk/Benefit Ratio:	Each of these flight rules could be broken by real time decision making after assessing the crew status and risk of delay to the Orbiter, crew, and mission.
Efficacy:	No situation has arisen yet that required EVA before Flight Day 3. Most crews have performed well enough to complete activities that were critical early inflight. Increased mistakes have been noted by crew members on Flight Days 1 or 2 and they often cross check with each other on critical tasks.
Cost-effectiveness:	No cost
Operational ease of use:	Easy to implement
Interference with other countermeasures:	None

Recommendations:

Continue present approach for scheduling timeline.

E DEVELOPED, ANECDOTAL, NOT ROUTINELY IMPLEMENTED

EARLY SHUTTLE PHASE

CM # 1. PREFLIGHT ADAPTATION TRAINING (TTD AND DOME)

Rationale:	Exposure to training using visual-vestibular mismatch, such as PAT, will facilitate adaptation to microgravity and reduce SMS.
Supporting Research:	A large number of ground-based studies have been performed to develop the stimulus conditions and training schedules which support the rationale.
Risk/Benefit Ratio:	Risk is very low, benefit is potentially high in reducing SMS.
Efficacy:	Preliminary results indicate that education, demonstration of and experience with novel perceptual phenomena in PAT devices led to an overall 33% improvement in SMS symptoms.
Cost-effectiveness:	Training devices and adaptation protocols have already been developed, i.e. no development costs. The training requires minimal crew time.
Operational ease of use:	All training is completed preflight. The only inflight activity would be recording information concerning evaluation criteria.
Interference with other countermeasures:	There are no known or predicted problems with interference with other countermeasures. There is a recognized potential for training procedures to produce some motion sickness symptoms; the current incidence rate in ground-based studies is 5-10% (interference with crew comfort).

Recommendations:

Improve and develop predictors of who will get the greatest benefit; customize training for individual crew members.

F DEVELOPED, ANECDOTAL, NOT ROUTINELY IMPLEMENTED

EARLY SHUTTLE PHASE

CM #S2 AND 3. UNUSUAL ATTITUDE EXPERIENCE *Anecdotal reports indicate that many crewmembers engage in a variety of activities involving exposure to unusual visual-inertial environments prior to a mission. Included among these are training in the WETF, training or other activity during parabolic flight in the KC 135 aircraft, performance of aerobatic maneuvers in high performance aircraft, SCUBA diving, PAT DOME training, and so on. This activity is based partly on anecdotal reports that pre-mission experience in unusual environments facilitates adaptation to prolonged microgravity.*

Rationale:	Suggested benefits from unusual environment experience is consistent with the view that coping with potential stressors can be facilitated by prior development of appropriate strategies and expectations
Supporting Research:	Crew debriefs, crew reports
Risk/Benefit Ratio:	Risk is very low, benefit is potentially high in reducing SMS.
Efficacy:	Anecdotal reports suggest alleviation of early SMS, but this has not been demonstrated
Cost-effectiveness:	Modest cost
Operational ease of use:	Modest increase in preflight training.
Interference with other countermeasures:	None identified

Recommendations:

Increase exposure to unusual attitudes using the WETF, parabolic flight, SCUBA diving and acrobatic flight in high performance aircraft. Unusual attitude experience should be recorded and correlated with SMS and other disturbances.

Identification of crewmembers likely to benefit from unusual attitude experience, as well as those likely to suffer negative consequences, should be attempted.

G TRIED AND ACCEPTED COUNTERMEASURES

SHUTTLE LANDING PHASE

CM # 4. CREW TRAINING / BRIEFINGS. *Crews are given briefings on observed problems (visual illusions, tilt/translation reinterpretation, locomotor instability, etc.) to be expected during the entry, landing, and post landing phases. Advised to limit head movements and to make slow body/head movements initially. Trained to rely on visual cues rather than “seat of the pants” during performance of landing tasks.*

Rationale:	Information about expected alterations and proposed coping strategies assists crew members in avoiding situations which cause symptoms and in dealing with vestibular abnormalities which occur.
Supporting Research:	Crew debriefs, crew reports
Risk/Benefit Ratio:	Minimal risk, moderate benefit
Efficacy:	Avoidance of provocative situations and use of other sensory modalities (e.g. vision, Orbiter instruments) partially prevent or compensate for vestibular problems.
Cost-effectiveness:	Minimal cost.
Operational ease of use:	Only minor changes in operational timelines or procedures.
Interference with other countermeasures:	No interference with other countermeasures.

Recommendations:

Continue to brief crews about expected changes in function and coping strategies. Update information based on ongoing crew debrief data and crew reports.

H TRIED AND ACCEPTED COUNTERMEASURES

SHUTTLE LANDING PHASE

CM # 5. RECENCY OF TRAINING (*Equipment is provided to enable crew members to practice those parts of the landing tasks which are possible close to flight and inflight.*)

Rationale:	Skill in performing nominal tasks necessary for landing improves the ability to perform these tasks when complicated by vestibular changes. The more recent the practice, the greater the skill.
Supporting Research:	Recent training in the IFR aviation flight environment has repeatedly been found to reduce accident rates.
Risk/Benefit Ratio:	Low risk, moderate benefit
Efficacy:	Crews report enhanced performance after proficiency training.
Cost-effectiveness:	cost of equipment purchase and maintenance, training time, and on orbit operation/practice judged effective by crews and managers.
Operational ease of use:	Minor timeline impact
Interference with other countermeasures:	None

Recommendations:

Continue to provide crews with adequate training close to flight and in-flight on tasks required during and after landing.

I TRIED AND ACCEPTED COUNTERMEASURES

SHUTTLE LANDING PHASE

CM # 6. OPERATIONAL RECOMMENDATIONS. *To the greatest extent possible, and in keeping with other operational requirements, landings are planned in such a manner as to decrease the chances of causing vestibular problems or being unable to compensate for them. Examples include: selecting runway with best visual cues, flying a low G HAC, selection of crew members best suited to perform landing tasks (e.g. who have landed the Shuttle after shorter duration flights without difficulty).*

Rationale:	Preventing, as much as possible, situations which contribute to vestibular problems lessens the chance of operational difficulties.
Supporting Research:	
Risk/Benefit Ratio:	Minimal risk, some benefit
Efficacy:	When they can be implemented these preventive measures lessen but do not eliminate vestibular derangement.
Cost-effectiveness:	Some cost impact to some recommendations (e.g. landing at Edwards vs. KSC) but judged appropriate.
Operational ease of use:	No major impact to operations
Interference with other countermeasures:	None with other countermeasures, some with other flight requirements.

Recommendations:

Continue to modify operational landing requirements to create best “vestibular” environment based on what is currently known and augmented with data that becomes available.

J TRIED AND ACCEPTED COUNTERMEASURES

SHUTTLE LANDING PHASE

CM # 7. INFLIGHT EXERCISE. *Proper use of exercise inflight to maintain strength and performance of antigravity muscles aids in locomotion postflight.*

Rationale:	Disuse atrophy of antigravity muscles adds to the locomotor instability seen post landing.
Supporting Research:	Greenisen study on aerobic capacity.
Risk/Benefit Ratio:	Low risk, good benefit.
Efficacy:	Exercise of proper muscles to the proper extent will prevent muscle deconditioning.
Cost-effectiveness:	Modest cost for providing proper equipment and on orbit time to exercise.
Operational ease of use:	Moderate overhead to set up equipment and perform adequate exercise.
Interference with other countermeasures:	Type of exercise chosen to prevent antigravity muscle loss may not be best to provide aerobic or skeletal fitness. Exercise may induce vestibular problems (SMS).

Recommendations:

Define best exercise protocols to prevent anti-gravity muscle loss or coordination deficits, and attempt to integrate with other exercise countermeasures.

K DEVELOPED, ANECDOTAL, NOT ROUTINELY IMPLEMENTED

SHUTTLE LANDING PHASE

CM # 4. MEDICATIONS DURING/AFTER ENTRY AND LANDING

Findings:

Rationale:	Vestibular suppressant medication should help relieve motion sickness symptoms on a short-term basis. Based on clinical use of these drugs for vestibular symptoms.
Supporting Research:	Multiple clinical studies showing efficacy of drugs in treating vestibular symptoms and motion sickness.
Risk/Benefit Ratio:	Risk is related to drowsiness side-effect of medication. In this environment the side-effect profile is low. Benefit of reduction of symptoms outweighs risks.
Efficacy:	Anecdotal reports from two to three crewmembers indicate that the nausea/vomiting are much improved.
Cost-effectiveness:	Very low cost (cost of a few pills). Used by crewmembers who do not have entry/landing tasks or after landing is completed.
Operational ease of use:	No or minimal impact on operations.
Interference with other countermeasures:	Potential interference with data for vestibular and cardiovascular studies postflight.

Recommendations:

Obtain data on actual use of medications during/after entry and landing. Determine individuals most likely to benefit from use of medications. Define criteria for use of post-flight drug use.

While meclizine, phenergan, and other medications are effective, over the last decade receptor antagonists specific for the H1 receptor have been developed. It is likely that at least one these (zamifenacen) may be successfully used to counter SMS without drowsiness as a side effect. Newer, more receptor-specific drugs should be evaluated for their potential to successfully treat post-flight symptoms without adverse side effects.

L DEVELOPED, ANECDOTAL, NOT ROUTINELY IMPLEMENTED

SHUTTLE LANDING PHASE

CM # 5. PILOT (*Laptop computer and hand controller provided to practice the landing tasks while on orbit.*)

Rationale:	Practicing certain portions of the landing tasks may improve ability to perform tasks with conflicting vestibular inputs.
Supporting Research:	Crew reports, debriefs.
Risk/Benefit Ratio:	Low risk, moderate benefit.
Efficacy:	Crews report improvement of skills.
Cost-effectiveness:	Moderate cost in providing hardware and crew training and on orbit time.
Operational ease of use:	Minor timeline impact.
Interference with other countermeasures:	None.

Recommendations:

Continue to use; improve landing task simulators.

M DEVELOPED, ANECDOTAL, NOT ROUTINELY IMPLEMENTED

SHUTTLE LANDING PHASE

CM # 6. HEAD MOVEMENTS DURING ENTRY *Crewmembers often perform head motions in pitch roll and yaw during entry and immediately post landing.*

Rationale:	Suggested benefits from active, voluntary head motion are consistent with an extensive research literature which demonstrates that voluntary action facilitates adaptation to sensory rearrangement and re-adaptation to nominal environments.
Supporting Research:	Crew reports, debriefs.
Risk/Benefit Ratio:	Low risk, moderate benefit.
Efficacy:	Anecdotal reports suggest re-adaptation may be facilitated by active head movements during entry. However, some crewmembers have reported that head movements induced or exacerbated disturbances.
Cost-effectiveness:	Modest cost
Operational ease of use:	Modest increase in preflight training.
Interference with other countermeasures:	None.

Recommendations:

Systematically collate and analyze crew de-brief data to determine the efficacy of head movements in re-adaptation.

Based on this data, as part of a DSO-type investigation, develop a standardized head motion protocol, record implementation of that protocol by crewmembers and correlate with postflight disturbance during structured debriefing.

Crewmembers should be familiar with their individual motion sickness syndrome pattern; entry/landing head motions should be terminated if they experience symptoms.

The efficacy of alternative protocols should be determined.

Identification of crewmembers likely to benefit from entry/landing head motions as well as those likely to suffer negative consequences should be attempted.

N DEVELOPED, ANECDOTAL, NOT ROUTINELY IMPLEMENTED

SHUTTLE LANDING PHASE

CM # 7. CREW ASSISTED EGRESS

Findings:

Rationale:	Less affected crew members can assist other crew members in an emergency egress.
Supporting Research:	
Risk/Benefit Ratio:	Potential risk to assisting crew member in delaying egress in order to help someone. Benefit is helping to ensure that all crew members egress in an emergency.
Efficacy:	Has not been needed or tried. Training on egress indicates that it is feasible.
Cost-effectiveness:	No cost involved.
Operational ease of use:	No or minimal impact on operations.
Interference with other countermeasures:	None
Interference with life:	None

Recommendations:

Egress training should include scenario of assisting an ill crew member out of the Shuttle. Define procedures or hardware changes to assist egress.

O DEVELOPED, ANECDOTAL, NOT ROUTINELY IMPLEMENTED

SHUTTLE LANDING PHASE

CM # 8. PREFLIGHT ADAPTATION TRAINING (PAT).

Rationale:	Pre-flight training to dual adapt the vestibular system to 0G and 1 G should decrease or prevent illusions and motion sickness during return to Earth.
Supporting Research:	Studies reported in the literature support the rationale for this training. A large number of ground-based studies have been performed that demonstrate “proof of concept” of adaptation and dual-adaptation in the PAT devices, and led to development of current training protocols and schedules.
Risk/Benefit Ratio:	Risk is low, and the potential benefits are high.
Efficacy:	The dual-adaptation training protocol has not been implemented and devaluated to determine efficacy.
Cost-effectiveness:	The simulators (trainers), training protocols and schedules have been developed. Minimal cost in crew time.
Operational ease of use:	No impact on inflight operations.
Interference with other countermeasures:	None known or anticipated. Minimal (5 - 10% incidence rate) of motion sickness symptoms associated with training in PAT devices.

Recommendations:

Develop and improve predictors of who will get the greatest benefit, and customize training for individual crew members.

P TRIED AND ACCEPTED COUNTERMEASURES

LONG DURATION RETURN

CM # 8. ASSISTED EGRESS

Findings:

Rationale:	Nominal procedure for egress of a crew member returning from a prolonged space station tour. Egress will be accomplished by ground personnel.
Supporting Research:	Reported by the Russians.
Risk/Benefit Ratio:	Risk could occur from delayed egress of crew member in a contingency. The benefit of ensuring safe nominal egress of crew member outweighs the unlikely necessity for rapid egress in a contingency.
Efficacy:	Russians have long history using assisted egress as their nominal procedure.
Cost-effectiveness:	Highly cost effective since it involves use of ground personnel only and no flight hardware development.
Operational ease of use:	No or minimal impact on operations.
Interference with other countermeasures:	None
Interference with life:	None

Recommendations:

Since the potential for an off-nominal landing is so remote, the use of assisted egress for a crew member returning from a prolonged space station tour seems to be the most efficacious approach. Post-flight symptoms of crew members returning from long duration flights should be monitored to see if they are qualitatively or quantitatively different from those seen on missions of shorter duration. As countermeasures are developed for the shorter duration missions, their applicability to longer duration missions should be assessed and implemented as required.

E - 3 Vestibular Task Group Supplemental Reports

Head Movement Monitoring/Dynamic Restraint/Training Systems

Astronaut head movements represent the dominant stimulus causing space sickness during the first few days of spaceflight, and reentry and postflight disorientation and earth sickness, which becomes more severe after longer flights. Astronaut head movements have been measured on some Spacelab and DTO missions, but the monitoring equipment has been too large and uncomfortable to be practical. There exists a need for improved, lightweight measurement technologies to monitor head and body position, orientation and movement to support a several types neurovestibular countermeasures.

Finding and Recommendation

NASA should exploit recent developments in miniaturized, solid state angular rate sensors (e.g. gyrochip) and linear accelerometers, by developing ultralightweight head motion monitoring technology usable for a variety of neurovestibular, biomechanical, and human factors countermeasure applications. The minimum system consists of a multiaxis ratesensor and linear accelerometer chip which attaches to the forehead via adhesive, or to a communications headset, and connected to a pocket battery/data processing package. A data port to a compatible IR telemetry system would be provided.

Three potential neurovestibular countermeasures are recommended for further study:

- Preflight head movement training system.

System which teaches crewmembers to automatically restrict their head movements, particularly in pitch and roll, and develop new head/eye coordination strategies appropriate for the early days of 0-G. Useful for enforcing head movement restrictions in simulations of early mission days, and reentry/landing cockpit procedures.

- Early on-orbit head movement restriction system.

Device which monitors the accumulating "head movement dose", and provides early warning when a crewmember moves about too vigorously, particularly in pitch and roll, for too long a time early in the mission, and conversely could also be used in a training procedure to more rapidly adapt crewmembers to weightlessness. (Companion linear accelerometers worn on the chest could monitor the vehicle microgravity disturbance forcing functions when the crewmember is moving about.)

- Reentry/landing head movement monitoring system

Device worn within LES re-entry suit which monitors the head movements and actual orientation of the head and body of individual crewmembers vs. time, so illusions which occur and sickness which develops can be related temporally to the physical stimulus. A LED display keyed on G level and angular rate could be provided, to provide crewmembers when head movements can safely be made.

Finding and Recommendation

There exists a need for a new technology usable for measuring the angular orientation and/or position of ambulatory IVA or EVA crewmember's head and/or body with respect to the vehicle in order to determine the validity of the head movement hypothesis. Electromagnetic, optical, and GPS technologies appear to be impractical for most applications. New methods are under development in the VR industry, and should be evaluated for possible use on Shuttle and Space Station.

Vibro-Tactile Orientation System (VTOS)

VTOS Concept:

Terrestrial spatial orientation is maintained by three sensory systems (visual, vestibular and somatosensory) providing redundant/concordant information. In the dynamic aerospace environment, the only reliable source of information is that obtained visually. The VTOS has demonstrated the novel concept that spatial orientation can be continuously maintained by providing veridical aircraft or astronaut position/motion information through the underutilized sense of touch. The approach uses a torso harness fitted with a pattern of tactors (miniature vibrators) that continuously updates the operators awareness of orientation/motion. The tactile system can be connected to a portable sensor, or directly interfaced with shuttle/EVA instrumentation. Using this intuitive source of information pilots have flown aerobatics and approaches blindfolded!

Findings And Recommendations

Shuttle Landing: Although current data concerning landing accuracy show no correlation with mission length, such information should continue to be gathered and analyzed in order to identify pilot control issues which may arise in the future.

Emergency Egress: In the event of an emergency egress with reduced visibility (smoke or water) or unusual attitude the astronauts will be aware of their orientation. Additionally, it is feasible to provide directional cues to the exit.

EVA: Impaired situational awareness occurs due to difficulty in establishing visual contact with objects in the four to eight o'clock positions. Astronauts occasionally report a sense of falling when leaving the confines of the shuttle. These problems can be addressed by haptic presentation of position and velocity cues.

Sensory Illusions: The most serious vestibular illusions with respect to adverse control of the shuttle are the G-excess and otolith-Tilt-Translation-Reinterpretation illusions. By providing true translation and orientation information through the compelling channel of touch it may be possible to either prevent or reduce these potentially disastrous illusions.

Medications

While Space Motion Sickness (SMS) is currently treated with IM promethazine (a histamine receptor antagonist) and although the drug appears to resolve 90% of reported SMS episodes, there remain several issues with this drug.

Despite promethazine treatment, SMS continues to be a problem for approximately 10% of astronauts.

Promethazine produces sedation or drowsiness as a side effect, which typically requires the astronaut to be given the drug just before sleep. Thus, in case of an emergency, the astronaut must be aroused and will likely receive a CNS stimulant to overcome the drowsiness.

Current protocol uses IM injection, which because of the altered body fluid composition during space flight, slows its absorption and effect. Suggestions have been made to give the drug IV to more rapidly provide relief.

Finding And Recommendation

While promethazine is effective, this older antihistamine acts as a receptor antagonist at multiple histamine (H1 and H2) receptors. Over the last decade, receptor antagonists specific for the H1 receptor have been developed, and it is likely that one of these (Zamifenacen) can be successfully used to counter SMS without drowsiness as a side effect. It may be that this drug, or one like it, is more efficacious for SMS for a larger percentage of the population. It is noteworthy that more specific receptor antagonists are also available for the cholinergic muscarinic receptor, for which scopolamine has been previously targeted and used. Our overall recommendation is that, despite the current use of and satisfaction with promethazine, newer more specific drugs should be evaluated.

If promethazine continues to be used and quick arousal is necessary, we recommend the use of amphetamines in low doses to counter that drowsiness. While IM injection may have its problems, IV injections carry the potential risk of more severe side effects, as well as the risks of improper dosing due to the altered gravitational environment, needle stick of the operator, bleeding, and thrombophlebitis, etc. We recommend continued use of IM injection route.

Artificial Gravity

There is ample motivation for the development of and testing an artificial gravity rotating device to prevent the major physiological deconditioning associated with long duration space flight. The space station, which is to be largely devoted to investigation of the problems of human long duration flight, will eventually afford the opportunity to test a variety of countermeasures which could be used for a Mars exploration mission. Before embarking on the expensive research program associated with human artificial gravity in space it is important to assess the neuro-vestibular implications of this "ultimate countermeasure".

One of the considerations in choosing an artificial gravity design is the tradeoff between radius and rotation rate to achieve a given g-level at the rim. Human factors issues largely determine the rim velocity and g-level, whereas physiological requirements influence the choice of radius (for g-gradient), glevel and exposure time. Vestibular considerations come into play in two ways. First of all, an adequate artificial gravity stimulus, combined with active head movements and locomotion, would presumably avoid some of the problems leading to re-entry and post landing disorientation and postural instability, although it is possible that astronauts might not be able to adopt a successful "dual state" adaptation. Secondly, the vestibular disturbances associated with cross-coupled angular acceleration when making out-of plane head movements, or Coriolis accelerations when making radial or tangential head movements, can create intra-sensory conflicts leading to motions sickness. These accelerations are directly proportional to the artificial gravity rotation rate. It has been widely assumed that a rotation rate of 1-2 rpm is easily tolerated, and that adaptation by steps can bring tolerance up to 6 rpm. Further extension of the rate to 10 rpm may be possible, especially in weightlessness without the disturbance of the conflicting earth vertical acceleration, but need flight testing to prove its acceptability. (With a 10 rpm rotation rate 1-g requires about a 10m radius and 0.5 g's only about 5m.) In order to determine the minimum radius to make an artificial gravity device acceptable from the point of view of the neuro-vestibular system, as series of research activities are required. These should begin with ground studies using a short radius centrifuge to determine the radius, g-level and rotation rate to provide an acceptable environment for intermittent stimulation and to prevent bone, muscle and cardiovascular deconditioning. Other studies using a slow rotating room will be necessary to assess the human factors issues and the problems of adaptation schedules. Only after proving the feasibility of the concept should we proceed to space experiments, beginning with a small (4m diameter) human centrifuge which can be accommodated in the Space Station for intermittent stimulation. finally, if all signs are positive, the definitive studies for long duration protection would be carried out with a large (1 km) tethered Variable Gravity Research Facility designed to co-orbit with the Space Station.

Findings

Artificial gravity, as the "ultimate countermeasure" may be limited in rpm by vestibular constraints.

Ground based research using bed-rest models, can be used to evaluate short arm centrifuges.

Relatively inexpensive, but long duration, development and testing can begin now to support a future Variable Gravity Research Facility and to use the Space Station for countermeasure development.

Recommendations:

Begin short radius centrifuge studies to determine radius, g-level, exposure and rotation rate for acceptable and effective prevention of deconditioning.

Use slow rotating room to determine human factor constraints and adaptation schedules.

Begin feasibility study for small (4m diameter) human centrifuge for Space Station.

Plan for design of a large Variable Gravity Research Facility to validate artificial gravity as a long duration countermeasure.

Gravity Replacement Earth Adaptation Training ("GREAT")

Findings

Currently, there are no proven counter-measures that will allow the neurovestibular system to function appropriately both in space and on Earth following space flight. Disruptions of perception, oculomotor control, psychomotor performance, posture, balance, and locomotion have been well documented both in-flight and post-flight.

Accuracy of performance in landing the shuttle, and rapid egress after landing have been identified as possible operational problems with potentially serious consequences. These problems most likely stem from changes in neurovestibular and sensory-motor integration that occur during space flight. Following long duration flights, these problems are exacerbated.

Recommendations

We recommend a study to determine the presence and seriousness of any operational consequences of spatial illusions or motion sickness during landing. If these prove to be of concern, then we suggest a ground study to test the practicality, acceptability and efficacy of intermittent exposure to a very short arm (1.0 meter) centrifuge, exposing the subject to primarily x-axis acceleration. If both of these studies support further work, we recommend subsequent development of a proposed countermeasure based on performing active head movements in an artificial gravity environment created by a short (approximately 1.0 meter) radius centrifuge. This will be accomplished by intermittently exposing crew members to centrifugation at 1.0 Gx while they make pitching head movements about an axis that is parallel to the axis of rotation.

The proposed countermeasure is expected (1) to maintain adequate terrestrial sensory-motor functioning in space, while simultaneously allowing for adaptation to the micro-gravity environment, and (2) to prevent debilitating neurovestibular effects, while simultaneously allowing for appropriate functioning upon return to Earth.

This countermeasure can be implemented using existing devices and those currently under development; it could be deployed in the shuttle middeck or in a Spacehab module, and it can be validated with existing information collected over the past several years. Although an integrated countermeasure for simultaneous resolution of cardiovascular, musculoskeletal, and neurovestibular problems, utilizing a larger radius centrifuge, may be developed in the future, the proposed effort will provide results that can be used sooner to develop specific operational solutions for the neurovestibular problems.

APPENDIX F

BEHAVIOR AND PERFORMANCE WORKING GROUP - SUPPLEMENTAL MATERIAL

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Other NASA representatives present included Drs. Harry C. Holloway, Arnauld E. Nicogossian, Joan Vernikos, and Guy C. Fogleman. USRA staff present included Dr. Kenneth Hart, Ms. Sandra L. Adamson, and Dr. David Liskowsky.

F - 2 Detailed BP Countermeasures Research Priorities

- A. With respect to psychiatric issues
- analyze the epidemiology and natural history of psychiatric illness in transplanted populations, deployed populations, and separated families
 - validate monitors preflight, inflight and postflight that improve objective assessment of essential behavior and performance factors in flight
 - identification of neural mechanisms, neurotransmitters, neural substrates that impact on optimal psychological performance: especially in areas of mood, well-being, motivation, reward
 - Research on the behavioral side effects of pharmacological countermeasures
 - study of circadian physiology and biochemical indices during spaceflight and their implications on the quality of rest and performance
 - development of proven methods for defining circadian cycles of humans that requires less intrusive implementation
- B. With respect to individual psychological development:
- develop a methodology to measure performance of meaningful tasks essential to mission safety and mission completion that is transparent to crew daily work
 - Assessment of job satisfaction for mission, ground and families of, mission crews.
 - Methodologies to quantify task errors (e.g. eye-hand coordination, visual memory of scenes, orientation of self and objects)
 - Research on cognitive processing, emotion, age and gender with respect to space missions
 - Research on the effect of noise, crowding and light on the health, sleep patterns, and mood of space mission and related crews.
 - Research on the effects of the space mission environment on sensory systems, motor systems and the cognitive process that enable them.
- C. With respect to group psychological development:
- Analysis of how healthy cultures are developed for small groups on space missions
 - Research on how leadership skills, command and control are developed and applied over the course of a space professional's career.
 - Research on group dynamics with respect to space missions
 - Research on communications and language with respect to international missions.

F-3 Report of the Behavior and Performance Working Group

The Behavior and Performance Working Group met Wednesday May 22, 1996 and Thursday May 23 1996. After being addressed by both US and Russian Astronauts and Cosmonauts the BPWG prepared the following analysis and recommendations.

Section 1

Identify Research Requirements

RECOMMENDATIONS

Areas of Focus

1. Decreasing task errors

Identify task errors in a measurable way

Analyze error patterns;

e.g., eye-hand coordination, visual memory of scenes, orientation of objects, cognitive skills, coordination skills

Human factors engineering or Behavior and Performance Principles research to “Design out” error

Human factors engineering or Behavior and Performance Principles training to “Design out” error

Embedded tests of performance for feedback to Mission team during the mission including on board simulation of emergency procedures

On board simulations to maintain task skills, especially those used later in the mission

Analysis of components of performance skills for critical tasks in various crew positions to develop a standard for behavior patterns

Study and define the current “Astronaut culture”

Study how healthy cultures are developed for small groups in isolation and confinement on physically challenging, long duration scientific missions

2. Reducing group conflict

Feedback on individual and group performance be provided to those who select astronauts and astronaut teams.

Use professional psychologists to observe, record, feedback and lead discussion on group interactions (crew, crew and ground, crew and family, family and ground)

Obtain self reports on status of crew interaction, social dynamics and structure

Strengthen mission crew - ground crew relationship through training including sections on conflict resolution, communication skills (active listening), etc.

Train ground and crew teams in full group environments with the individuals who will be involved.

Study the use of games as a tool to work out intra crew interactions (cross-cultural, new technology, environmental hazards, work schedules)

3. Increasing job satisfaction

Assess current sources of job satisfaction for mission crews, ground crews, other groups of NASA employees, families of mission crews

What sources are similar and which are different compared to other organizations

- How does NASA identify and reward desirable behavior and performance for astronauts?
- What other forms of identification and rewards are possible and desirable?
- How does NASA identify and discourage undesirable behavior and performance for astronauts?
- What other forms of identification and discouragement are possible and desirable?
- What are the current sources of dissatisfaction for astronauts?
- How can these dissatisfactions be addressed?
- Is there a track for career astronauts?
- Why do experienced Astronauts leave NASA?
- Is this desirable or not?
- 4. Accomplishing scientific and other mission goals
 - How to measure success ?
 - Quantify DTOs, DSOs, technology goals, organizational goals, political goals
 - Develop metrics for scientific research
 - Publications in peer reviewed journals, prestigious peer selected awards (Nobel prize, etc.), citations in peer review journals
 - Develop metrics for Astronaut Corp (non-technical) that are mission dependent (i.e. there is a difference between long duration and short duration missions)
- 5. Maintaining personal health, well being and social cohesiveness
 - Employ professional psychologists to help individuals define and maximize performance for personal/professional mental and physical health goals
 - Employ social or clinical psychologists or other professionals with special training or experience in cross cultural work to help space mission planners and teams define and maximize performance

Section 2

Overarching scientific strategy

RECOMMENDATIONS

Assess the status of basic and applied behavioral science research for planned space missions (preflight, flight and postflight for Space Crews, Ground Crews and Families of Crews) with respect to: selection, training, prevention, intervention, monitoring, evaluation and postvention for planned space missions. The research is transdisciplinary and addresses the interrelationships between psychosocial, cultural and human factors.

Section 3.

Psychosocial factors that are relevant to the Shuttle-Mir, analog, and International Space Station environments include crew composition and selection, ground-crew interaction, workload and its association with personal autonomy and control and individual mood, isolation and from and the ability to cope with both mundane and unexpected events and circumstances, the relationship between crew members and their organizations both pre-flight and in-flight, and the differential access to support and resources among crew members.

Cultural factors include the organizational cultures involved in these settings, the culturally-influenced set of expectations and norms that regulate social interaction, including social support and rules of conflict, and language and cultural differences that influence the ability of crew members to communicate with one another both formally and informally.

Human factors include the influence of workload on individual and group performance, time allocation, training, and opportunity for exercise and leisure activities; and the influence on environmental conditions (noise, crowding, storage, light) on health, sleep patterns, mood, and task performance.

RECOMMENDATIONS

Research should be conducted on psychosocial, cultural and human factors relevant to the Shuttle-Mir, analog, and International Space Station.

Research should be conducted to determine if human behavior and performance in the Shuttle Program, Shuttle Mir Space Program, and International Space Station are related in a fixed relationship regardless of environmental context or if they represent qualitatively different experiences that limit our ability to generalize from one experience/environment to the next.

Section 4.

All behavior and performance research conducted as part of NASA's Life Sciences Program should involve a demonstration of the relationship between the critical questions addressed by the research and more fundamental questions related to human behavior and performance in general. For instance, research conducted on a manned space mission or space analog offers the potential of determining the extent to which state or train characteristics influence behavior and performance. Similarly, the extent to which crew member autonomy or control over workload influences health, well-being and performance could provide greater insight into the role of self-efficacy and personal autonomy on human behavior and performance in general. Ultimately, research on behavior and performance in long-duration space missions should be designed and developed that meets and needs of the larger society for a greater understanding of behavior and performance as well as the more specific, programmatic needs of NASA and other national space agencies.

RECOMMENDATIONS

1. Behavior and performance research conducted on long-duration manned space missions or analog environments with relevance to manned space missions should demonstrate a relevance to more fundamental questions of behavior and performance in general.
2. Research on behavior and performance for long-duration space missions should be designed to meet the needs of society at large, providing a greater understanding of behavior and performance as well as addressing the more specific, programmatic needs of NASA and other national space agencies.

Section 5.

Should research be conducted with space crew members themselves or with analog populations?

RECOMMENDATIONS

1. Priority should be given to analog studies for understanding behavior and performance during long-duration human space missions. Astronaut time is a scarce, valuable resource. To preserve that resource, specific justification for the need to have astronaut time should be required, as well as evidence of appropriate ground work.
2. Justification must be provided as to why a particular study should be conducted in space.
3. Proposals must also demonstrate the likelihood that data will be collected in a valid and reliable manner given the unique conditions of human missions and the organizational cultures involved.

Section 6.

The BPWG should provide programmatic oversight into the human behavior and performance research program at NASA. Such oversight is considered critical to accomplishing the goals and objectives as outlined in the WG Charter and in order to avoid redundancy in requirements definition. This oversight would involve assistance in the proposal review process, review of scientific guidelines, and evaluation of the products of NASA-funded behavior and performance research.

RECOMMENDATIONS

1. The BPWG should provide NASA Life Sciences with names of qualified individuals who could be used to review research proposals either as a panel or on an ad hoc basis. The BPWG recommends that members of the astronaut community be included in this review process, to insure that proposals are feasible and likely to produce valid and reliable data.
2. The BPWG should be given access to technical reports and publications resulting from NASA-funded research to determine whether program goals and objectives are being addressed and whether new requirements should be developed.
3. The BPWG should continue with its current membership to provide support to the Program Coordinator for Behavior and Performance, addressing the charter of the Behavior and Performance Working Group.

GENERAL RECOMMENDATIONS

1. Research Programs to Emphasize
 - A. Analysis of analog environment data with emphasis on commonality of lessons learned. Include full range, from laboratory studies at JSC to full up analogs in the Antarctic, or submarines.
 - B. Work with Russian data, psychologists, psychiatrists; analyze their technique and experience: how they interview, test, select, (out and in), train, monitor, support, integrate crews, deselect. How did and do the Russians validate and refine their process? What did they try and discard? And why? What have they not tried? And why? A great deal of this work has already been done and the work needs to be integrated with current behavior

and performance countermeasures. Activity in this area could be a prelude for a specific researcher who is interested in training or selection.

C. Follow up for 1990 Rose-Helmreich study and cohort on selection of US Astronauts to assess the effectiveness of the research and to validate current and possibly future selection criteria and methods

2. Before research is carried out on astronauts careful consideration should be made as to whether or not the same research could be carried out on the ground in another environment such as a laboratory or analog environment. Previous research has documented a number of analog environments that have already offered or are offering the potential of providing a greater understanding of human behavior and performance during long-duration missions in space. Research should be conducted which moves beyond a description of each of these analog settings and a comparison of the extent to which these do or do not resemble long-duration manned space missions. This research should begin with a set of specific questions and then determine whether they can or cannot be answered with data already available (such as MIR or Skylab data) or data potentially available from an analog setting. Efforts should be made to provide answers to these questions with existing data or to conduct research in these analog environments that will provide answers to these questions.

3. Research should be conducted which describes the current organizational cultures which affect behavior and performance during human space missions. These organizational cultures are comprised of a system of norms, understandings and meanings that are shared and distributed among the members of an organization. In addition, research should be conducted that defines an optimal organizational culture for decreasing task errors, reducing group conflict, increasing job satisfaction, accomplishing mission scientific goals, and maintaining personal health, well-being and social cohesiveness. An optimal organizational culture should promote strong leadership and adherence to a common set of understandings, meanings and norms, while simultaneously promoting flexibility and individual autonomy.

4. Research should be conducted into procedures and methods for selection into the astronaut corps and formation of crews for specific flights by each national space program. Research should also be conducted that defines optimal procedures for screening in astronauts best qualified for performance in specific circumstances in specific crews.

5. Research should be conducted that will enhance individual performance, group performance and leadership. This research should identify the criteria necessary to evaluate performance and the methodology for both active and passive forms of training and countermeasures. Passive countermeasures include monitoring of individual and group behavior and performance pre-flight and in-flight, while active countermeasures include interventions designed to train personnel pre-flight and prevent decrements in performance in-flight. Research is also required to determine whether active interventions can be implemented using existing programs and protocols or whether entirely new interventions that are specifically designed to address the unique conditions and requirements of human space missions should be developed. A full range of problems need to be addressed from circadian rhythm to work volume (too much or too little).

6. Assessment of inflight hardware and software support is needed to supplement training, group development and dynamics, as well as individual cognitive and emotional health.

7. Assessment of time and task management methodologies are necessary for inter and intra group performance in both flight and ground teams.
8. Research on gender with respect to behavior and performance on space missions needs to be assessed with respect to space crews, ground crews, families.
9. Assessment of physiological and pharmacological countermeasures with respect to behavior and performance is necessary across a spectrum of challenges from pharmacological agents to neutralize Space Motion Sickness, exercise as a psychological countermeasure to some of the negative effects of microgravity, etc.
10. Assessment of the right amount of training is critical to avoid under or over training.
11. Assessment of leadership training and opportunities as part of the career path of astronauts is necessary